THE CATALYTIC OXIDATION OF ORGANIC SUBSTRATES UTILIZING MOLECULAR OXYGEN AND PEROXIDES

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

1993

ACKNOWLEDGEMENTS

I would like to express my deepest appreciation to the people who are closest to me. My wife and best friend, Lynn, has provided me with a love and support for which I am forever indebted. She has always been there for me during the "thick and thins" of graduate school. Also, I would like to thank my families, both here in Florida and in Georgia, for their support and encouragement.

Many thanks are also due to the many people at Auburn University for their advice and guidance in furthering my career in the area of chemistry.

Also, I would like to express my appreciation to Dr. Russell S. Drago for his constant help, understanding, and enthusiasm for my pursuit of a career in chemistry. Without his advice and guidance, this work would have not been possible.

Many thanks are due to Dr. Robert C. Stoufer, Dr. James M. Boncella, and the remainder of my supervisory committee for their help and encouragement in making this work easier.

I would also like to thank the members of the Drago Group for their help and suggestions in my research.

Many thanks are due to the remainder of the inorganic division for their help and support.

A special thank you is due to Mr. Charles W. Cromwell for his advice and assistance in obtaining the right chemicals.

Last, but by no means least, I would like to thank the many other people in the chemistry department who helped me in accomplishing this work.

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KEY TO ABBREVIATIONS AND SYMBOLS

Abbreviation or Symbol	Definition
acac	acetylacetonate
α	alpha carbon
β	beta carbon
^{13}C	carbon-13
$^{\circ}C$	degrees Celsius
δ	chemical shift
DEGS	diethylene glycol succinate
DIPT	diisopropyl tartrate
DMA	dimethylacetamide
DMF	dimethylformamide
dmp	2,9-dimethyl-1,10-phenanthrolene
dmso	dimethylsulfoxide
E/B	epoxide to benzaldehyde
ee	enantiomeric excess
EtOH	ethanol
FID	flame ionization detector
γ	gamma carbon
GC	gas chromatograph
g	grams

Abbreviation or Symbol	Definition
g/cm^3	grams per cubic centimeter
^1H	proton
hfacac	hexafluoroacetylacetonate
hrs.	hours
M	molarity
MA	maleic anhydride
MHz	megahertz
min.	minutes
mL	milliliters
MS	methylstyrene
nm	nanometers
NMP	1-methyl-2-pyrrolidinone
NMPD	1-methylpyrrolidine
NMP-5-OOH	5-hydroperoxo-1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
OAc	acetate
octoate	2-ethylhexanoate
O/S	oxidant to substrate
^{31}P	phosphorus-31
pfb	perfluorobutyrate
ppm	parts per million
%	percentage
psig	pounds per square inch
ROOH	alkyl hydroperoxide
R_2SO	sulfoxide

Abbreviation or Symbol	Definition
R_2SO_2	sulfone
SG	silica gel
t-BuOOH	t-butyl hydroperoxide
TMS	tetramethylenesulfone
TPP	tetraphenylporphyrin
UV/vis	ultraviolet/visible
V/V	volume per volume
ω	omega carbon

Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

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August, 1993

Chairperson: Russell S. Drago
Major Department: Chemistry

The use of 1-methyl-2-pyrrolidinone in a catalytic cycle employing molecular hydrogen and oxygen in the presence of transition metal catalysts is described. Under mild conditions, this catalytic cycle provides a regenerative N-alkylamide hydroperoxide for organic substrate oxidations.

Under mild conditions, the ability of the N-alkylamide hydroperoxide, 5-hydroperoxo-1-methyl-2-pyrrolidinone, to oxidize alkenes and thioethers is investigated in the presence of transition metal catalysts. Mechanistic pathways for these metal-catalyzed reactions are presented.

Transition metal-catalyzed thioether oxidations are investigated under ambient conditions in 1-methyl-2-pyrrolidinone using the alkyl hydroperoxides, 5-hydroperoxo-1-methyl-2-pyrrolidinone and t-butyl hydroperoxide. These results were used to determine the role of the transition

metal catalysts in the N-alkylamide hydroperoxide system.

Using 1-methyl-2-pyrrolidinone, the activation of H_2O_2 by transition metal catalysts and/or the peroxyacid precursor, maleic anhydride, is investigated under ambient conditions. This oxidant exhibits an enhanced stability in 1-methyl-2-pyrrolidinone.

CHAPTER 1
GENERAL INTRODUCTION

The oxidative transformations of functional groups are basic to organic chemistry with oxidations being extensively used in the laboratory synthesis of fine organic chemicals as well as the manufacture of large-volume petrochemicals.[1] Industrially, the majority of the processes employed involve the use of transition metal complexes, using molecular oxygen, H_2O_2, and alkyl hydroperoxides as the primary oxidants. These catalytic processes are advantageous over their non-catalytic counterparts because they proceed efficiently under mild conditions leading to more energy efficient processes. Furthermore, catalytic processes are generally more selective, resulting in optimal utilization of starting raw materials. For the most part, catalytic processes are environmentally friendly for they involve small amounts of effluents, which are becoming increasing more difficult to dispose of. As a result, a greater emphasis must be placed on the development of new and improved catalytic processes for the oxidative transformations of organic substracts.

A major objective of this work is to present several potential applications of the industrially important solvent, 1-methyl-2-pyrrolidinone, in several catalytic processes. This biodegradable solvent possesses several other properties

that make it a desirable solvent for catalytic applications (Table 1-1).[2] 1-methyl-2-pyrrolidinone is completely miscible with water, lower alcohols, lower ketones, ether, ethyl acetate, chloroform, and benzene. It is moderately soluble in aliphatic hydrocarbons and dissolves both organic and inorganic compounds. In view of its high boiling point, many reaction products can be separated by distillation.

Recently, 1-methyl-2-pyrrolidinone has replaced other solvents of poorer stability, higher vapor pressures, greater toxicities, or more facile skin penetration. Large amounts of 1-methyl-2-pyrrolidinone are used in the polymer industry as a medium for polymerization and as a solvent for finished polymers; thereby, making this cyclic N-alkylamide a very important solvent for industrial chemical applications.

Table 1-1 Properties of 1-Methyl-2-pyrrolidinone.

Property	Value
freezing point	-24.4°C
boiling point	202°C
density	1.028 g/cm^3
flash point	95°C

CHAPTER 2
A REGENERABLE N-ALKYLAMIDE HYDROPEROXIDE FOR CATALYTIC SUBSTRATE OXIDATION

Introduction

The oxidation of amides to their corresponding imides has been reported in the literature for straight chain alkylamides and five- and six-membered lactams (cyclic amides).[3-9] Alkenes and ethers undergo a similar oxidation pathway in which a hydrogen atom is abstracted from a carbon atom that is adjacent to the double bond of the alkene or the oxygen atom of the ether.[10,11] Hydrogen atom abstraction from a carbon adjacent to a nitrogen atom in an amine has a rate constant much higher than those of alkenes and isostructural ethers. In the photooxidation of N-alkylamides, oxygen attack occurs on the methylene group adjacent to the amide nitrogen.[12] The oxidation of the straight chain alkylamides is characterized by autoxidation at the primary carbon atom of the hydrocarbon chain, while the carbon atoms in the ketone chain are not affected (Figure 2-1). In the case of the five- and six-membered lactams, the oxidation takes place at positions 5 and 6 in the five- and six-membered rings, respectively (Figure 2-1).

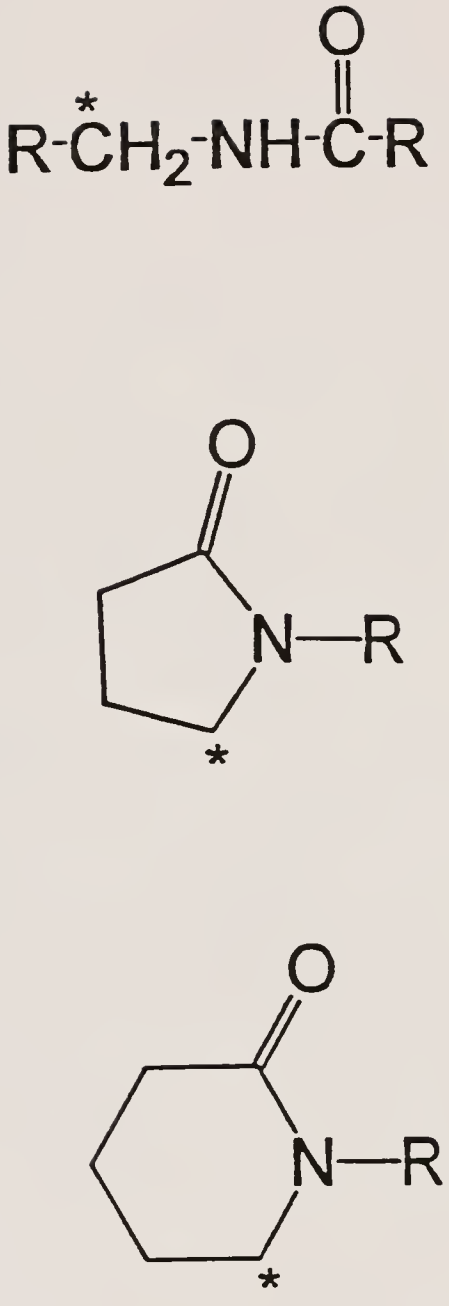


Figure 2-1 Positions of Autoxidation (*) of Various Amides.

The autoxidation of amides proceeds by a peroxy-radical mechanism similar to the amine autoxidation mechanism reported by Beckwith et al. (Figure 2-2); however, the oxidation of amides to their corresponding amine oxides does not occur because the nitrogen is a very weakly basic donor atom.[13] During this reaction, the most common oxidation product was the imide.[4,9] Needles and Whitfield attempted to oxidize five- and six-membered lactams with peroxysulfates to their ring-opened products, the ω-aldehydoamides; however, these reactions yielded imides as the products.[4] For example, the oxidation of 1-methyl-2-pyrrolidinone with peroxysulfate yielded N-methylsuccinimide. When reacted with equimolar amounts of ruthenium tetroxide, amides are again oxidized to their corresponding imides.[3]

The selective oxidation of amides to imides has been reported using alkyl hydroperoxides or peroxyacids in the presence of transition metal catalysts (i.e., Co(II), Mn(II), or Mn(III)).[9] The oxidations of 2-pyrrolidinone and 1-methyl-2-pyrrolidinone produced succinimide and N-methylsuccinimide, respectively.

Imides have been obtained by the electrochemical oxidations of their corresponding amides.[14,15] During some of these reactions, the amido-alcohol was produced.

The use of molecular oxygen in the autoxidation of amides has been shown to yield both the corresponding hydroperoxides

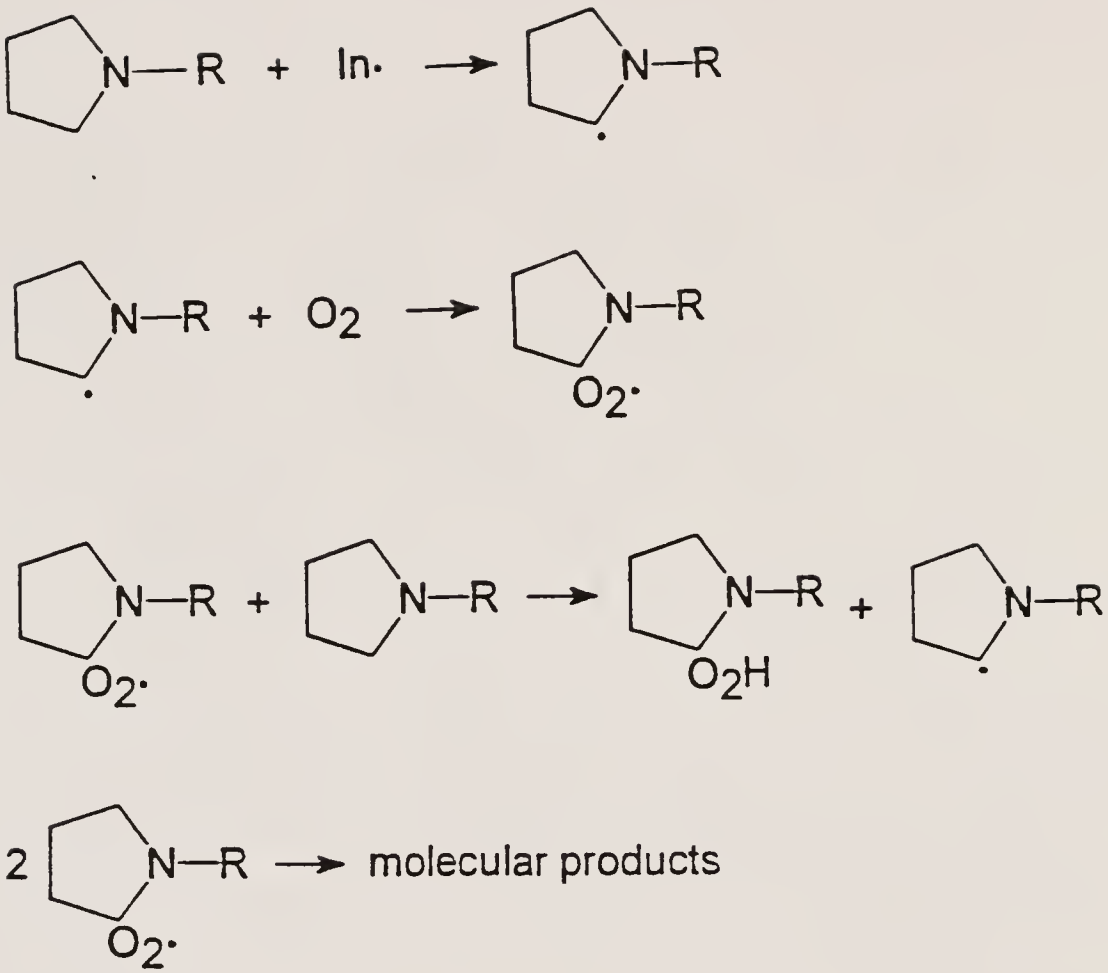
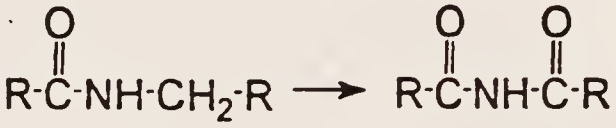


Figure 2-2 Amine Autoxidation Mechanism.[13]

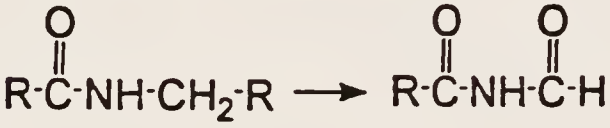
and imides. Using the catalysts, $KMnO_4$, the oxidation of 1-methyl-2-pyrrolidinone with molecular oxygen yielded N-methyl-succinimide.[16]

In a very thorough investigation into the autoxidation of various N-alkylamides, Lock and Sagar observed three principal overall reactions:[5]

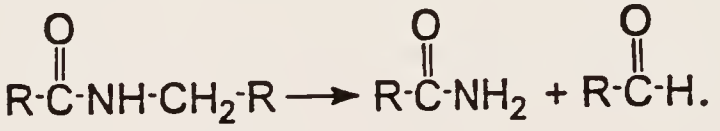
(1) Formation of N-acylamides from N-n-alkylamides:



(2) Formation of N-formylamides from N-n-alkylamides as a result of C_1-C_2 bond scission:



(3) Oxidative dealkylation to yield carbonyl compounds:



The autoxidation of the tertiary amide, 1-ethyl-2-pyrrolidinone, was performed at 131°C under molecular oxygen. The principle stable products were 1-acetyl-2-pyrrolidinone (8.1%), 2- pyrrolidinone (21%), and N-ethylsuccinimide (71%); thereby, indicating that attack is 2-3 times more probable at the ring methylene group adjacent to the nitrogen atom than at the exocyclic N-ethyl group.[5] No evidence for ring opening was observed. The formation of 1-acetyl-2-pyrrolidinone and

N-ethylsuccinimide can be explained by the decomposition of the hydroperoxides produced during the reaction. The formation of 2-pyrrolidinone is the result of an oxidative dealkylation process. The formation of these N-acylamides can be explained in terms of a peroxy-radical mechanism.[5,7] Abstraction of a hydrogen atom, from the carbon adjacent to the nitrogen atom, by an initiator, such as a 1-amidoalkoxy-radical from the breakdown of the amide hydroperoxide during thermal oxidation, or by an added radical initiator (i.e., t-butyl hydroperoxide, benzoyl hydroperoxide, or α,α-azobis(isobutyronitrile) (AIBN)) would result in the formation of the 1-amidoalkyl-radical, which would form the corresponding peroxy-radical by rapid reaction with molecular oxygen.[6,7] Depending on the reaction conditions, these peroxy-radicals may then either be removed from the system by mutual interaction or propagate a chain reaction by abstraction of a hydrogen atom from another molecule of the substrate. The kinetics of the autoxidation of these N-alkylamides initiated thermally or by radical initiators has established that the oxidation proceeds by a radical-chain mechanism analogous to the mechanism proposed by Beckwith for the oxidation of amines.[13] Furthermore, Sagar reported that radical initiators and transition metal salts (i.e. Co(II), Cu(II), and Fe(III)) in low concentrations failed to increase the already low maximum hydroperoxide concentration.[6] Higher transition metal salt concentrations were found to greatly decrease the maximum hydroperoxide concentration due to the

accelerated decomposition of the hydroperoxides by the transition metal catalysts.

From the experimental evidence presented, it can be inferred that the thermal oxidation of the amides proceeds by a peroxy-radical mechanism. Both the hydroperoxides and the other observed products in these thermal oxidations can be explained in terms of the peroxy-radical mechanism and subsequent heterolytic decomposition of the hydroperoxides produced during the reactions.[6]

More recently, the uncatalyzed oxidation of 1-methyl-2-pyrrolidinone by molecular oxygen under mild conditions (O_2 (50psig), 75°C) was found to form an approximate 2M concentration of an oxidizing agent, which was characterized by various NMR (^{13}C and ^{1}H) and mass spectral methods to be the hydroperoxide, 5-hydroperoxo-1-methyl-2-pyrrolidinone.[17] In the presence of peroxide decomposition catalysts, such as $Co(BPI)_2$ (where BPI=1,3-bis(2-pyridylimino)isoindolene) or Mn(TPP)Cl (where TPP=tetraphenylporphyrin), the hydroperoxide was converted to N-methylsuccinimide (Figure 2-3). These findings show that the hydroperoxide 5-hydroperoxo-1-methyl-2-pyrrolidinone, is the undetected intermediate for the reported oxidations of 1-methyl-2-pyrrolidinone to N-methylsuccinimide.

Another interesting aspect of the chemistry of amides and imides is the difficulty of hydrogenating cyclic imides to their corresponding cyclic amides (lactams). Even thought Cramer observed the conversion of phthalimide to phthalimidine using a nickel catalyst at 200°C under 200-250 atm of

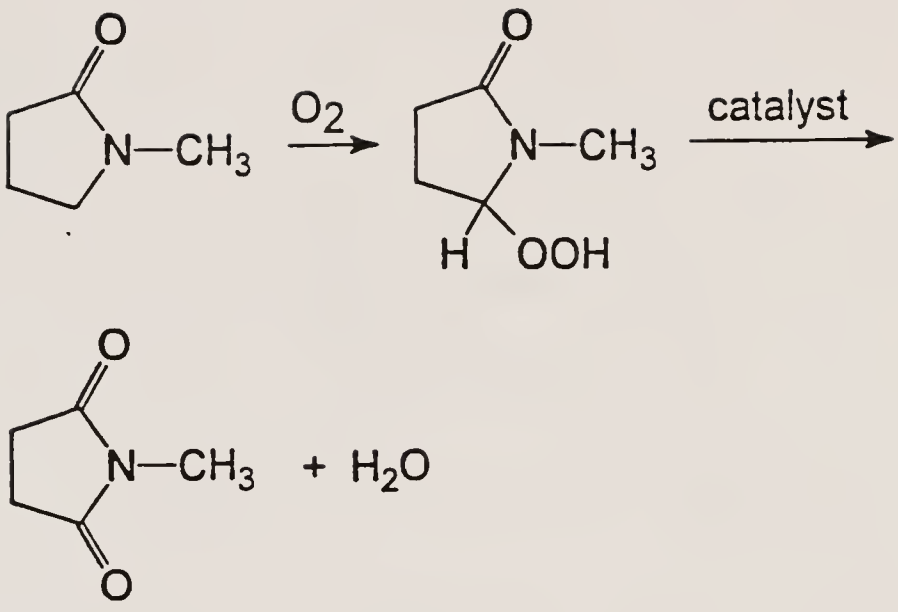


Figure 2-3 Metal-Catalyzed Oxidation of 1-Methyl-2-pyrrolidinone.

hydrogen, attempts to obtain a similar reaction with succinimide were not successful.[18,19] The carbonyl functionalities in phthalimide and succinimide are unaffected on attempted hydrogenation at room temperature and atmospheric pressure over a platinum oxide catalyst.[20] Attempts to hydrogenate N-methylsuccinimide to 1-methyl-2-pyrrolidinone with this catalyst at 75°C under 55psig of hydrogen were only marginally successful with only small amounts of 1-methyl-2-pyrrolidinone being detected after 264 hours of reaction.[21] Hydrogenation of the imide ring in these compounds can be accomplished under such mild conditions if an acetyl or other acyl group is attached to the imide nitrogen atom.[20]

Based on the reported results for the hydrogenation of a series of cyclic anhydrides and cyclic imides, McAlees and McCrindle proposed a mechanism for the hydrogenation of cyclic anhydrides and imides at the catalyst surface (Figure 2-4).[20] The initial step (i) involves the nucleophilic attack of the catalyst on an imide (or anhydride) carbonyl carbon atom of the substrate molecule absorbed on the catalyst surface on its less-hindered side (species I) with concomitant ring opening to produce species II. This acyl group cleavage step is followed by the hydrogenolysis of the metal-carbon bond to give the aldehydo-functionality, followed by rotation of this functionality through 180° to give a species absorbed through the aldehyde carbonyl oxygen atom step (iii). Ring closure of the aldehydo-intermediate gives an oxygen-bound species (IV). The rate of this step compared with the rate of further

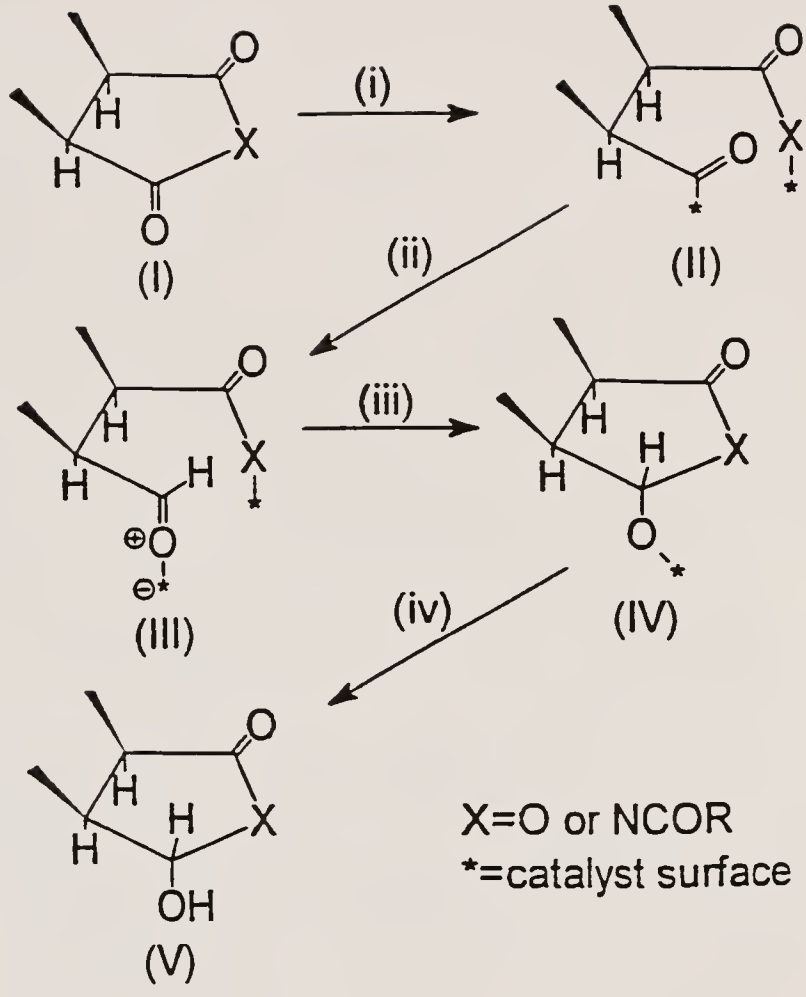


Figure 2-4 Catalytic Hydrogenation Mechanism for Cyclic Anhydrides and Imides.[20]

hydrogenation of the aldehydo-functionality generated in step (ii) may determine whether products of further reduction are obtained. Thus, for the N-acylsuccinimide series, where ring closure would be expected to be slower since the aldehydo- and imide groups of the intermediate (III) are not rigidly unstrained in a manner favoring interaction, the main product is an alcohol, or products derived therefrom. Hydrogenolysis of the oxygen-bound species (IV) and desorption gives a hydroxy-lactone or hydroxy-lactam, which can undergo further hydrogenolysis by a similar pathway to give the corresponding lactone or lactam.

The reduction of succinimide to the corresponding amide, 2-pyrrolidinone, was accomplished in the presence of ammonia using a catalyst, such as cobalt, nickel, palladium, platinum, or ruthenium, supported on carbon or silica gel.[22] Another reported process for preparing 2-pyrrolidinone involved the reduction of succinimide in an aqueous system in the presence of a supported palladium catalyst.[23] High pressures of hydrogen and elevated temperatures are required for these processes.

Results and Discussion

Our interest in the oxidation and hydrogenation reactions of N-alkylamides involved using 1-methyl-2-pyrrolidinone catalytically in a cycle that used only molecular hydrogen and molecular oxygen to effect mono-oxygenate type substrate oxidation. 1-methyl-2-pyrrolidinone reacts with molecular

oxygen to form the corresponding hydroperoxide, 5-hydroperoxo-1-methyl-2-pyrrolidinone, which can be used to selectively oxidize a variety of organic substrates producing N-methylsuccinimide as a byproduct (Figure 2-5, path(a)).[24] Hydrogenation of N-methylsuccinimide would regenerate 1-methyl-2-pyrrolidinone allowing it, in effect, to function as a catalyst for the oxidation of organic substrates using only molecular hydrogen and molecular oxygen under mild conditions.

The preparation of 5-hydroperoxo-1-methyl-2-pyrrolidinone from the direct reaction of 1-methyl-2-pyrrolidinone and molecular oxygen at 75°C makes it an inexpensive, easily obtainable source of hydroperoxide.[25] It was of interest to compare the stability of this hydroperoxide with a commercially available hydroperoxide. The stability of a solution of 5-hydroperoxo-1-methyl-2-pyrrolidinone was compared with a t-butyl hydroperoxide solution of comparable hydroperoxide concentration under ambient conditions by iodometric titration. As seen in Figure 2-6, the stability of 5-hydroperoxo-1-methyl-2-pyrrolidinone, a secondary hydroperoxide, is comparable to that of t-butyl hydroperoxide, a tertiary hydroperoxide.

Generation of the Hydroperoxide

An improved synthesis of 5-hydroperoxo-1-methyl-2-pyrrolidinone involves increasing the conversion of 1-methyl-2-pyrrolidinone to this product and eliminating the induction period. A series of experiments were carried out to

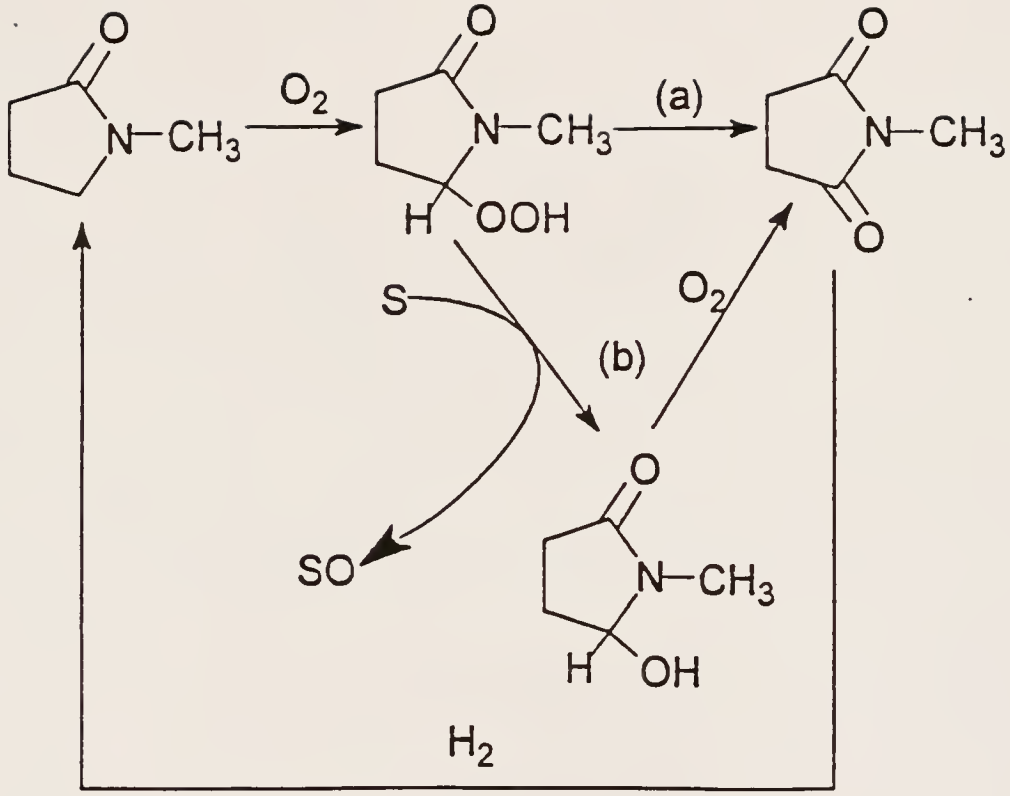


Figure 2-5 1-Methyl-2-pyrrolidinone Catalytic Cycle.

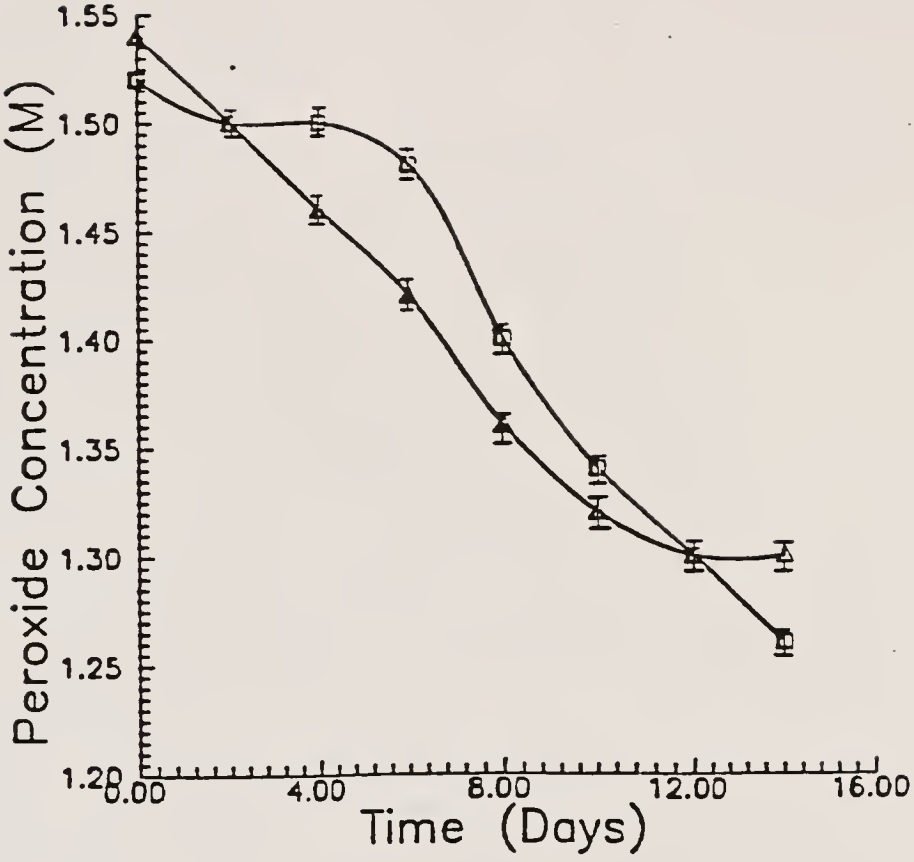


Figure 2-6 Comparision of 5-Hydroperoxo-1-methyl-2-pyrrolidinone (Δ) and t-Butyl Hydroperoxide (□).

accomplish these objectives. The formation of hydroperoxide as a function of time is shown in Figure 2-7 for the uncatalyzed direct reaction with molecular oxygen. An autoxidation mechanism is suggested because of the observed induction period.

As shown in Figure 2-7, the hydroperoxide reaches a maximum concentration at approximately 2 M. The reaction of 1-methyl-2-pyrrolidinone with molecular oxygen (50 psig) at 75°C was analyzed at various time intervals by ^{13}C and ^{1}H NMR, along with iodometric titrations. The integrated ^{1}H NMR spectra and the corresponding iodometric titrations of the periodically drawn samples showed that the hydroperoxide concentration remained constant after 48 hours, but the concentration of N-methylsuccinimide increased steadily. A steady-state hydroperoxide concentration is attained in this system when the rates of hydroperoxide formation and decomposition become equal.

An attempt was made to decrease the observed induction period by carrying out the reaction of 1-methyl-2-pyrrolidinone with molecular oxygen (50 psig) for 4 hours at 100°C and then decreasing the temperature to 75°C for the remainder of the reaction. Although the induction period was decreased using the higher initial reaction temperature, a lower maximum hydroperoxide concentration resulted.

The uncatalyzed reaction of 1-methyl-2-pyrrolidinone with molecular oxygen in the presence of other solvents (H_2O or CH_3CN) was investigated to determine if any hydroperoxide

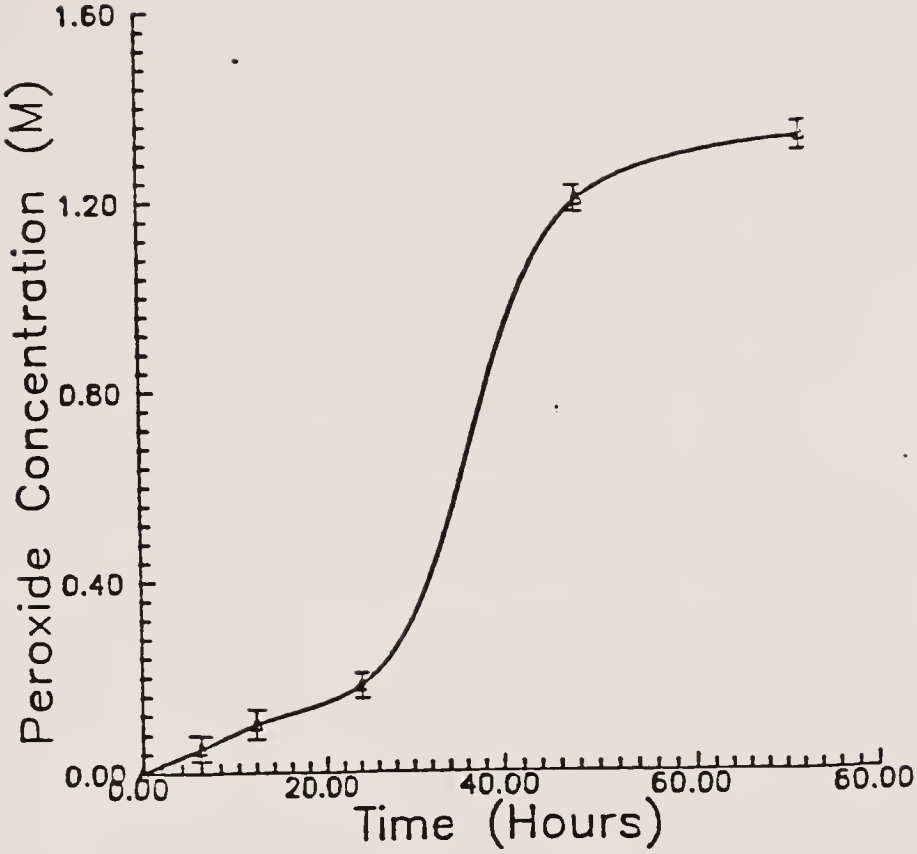


Figure 2-7 Formation of 5-Hydroperoxo-1-methyl-2-pyrrolidinone.

formation would occur. Both systems were found to form the corresponding hydroperoxide; however, a lower steady-state hydroperoxide concentration was attained than observed in the oxidation of neat 1-methyl-2-pyrrolidinone (Table 2-1).

Experimental results given in Table 2-1 indicate that formation of the hydroperoxide, 5-hydroperoxo-1-methyl-2-pyrrolidinone, in the solvent, CH_3CN, proceeds more readily than in H_2O. In pure 1-methyl-2-pyrrolidinone, 20% of the 1-methyl-2-pyrrolidinone is converted to the corresponding hydroperoxide at steady-state conditions. In the 50/50 and 10/90 1-methyl-2-pyrrolidinone/CH_3CN systems, 9% and 6% of the 1-methyl-2-pyrrolidinone were converted to the N-alkylamide hydroperoxide, respectively. In all solvents, after 72 hours of reaction, no further increases in the hydroperoxide concentrations were observed, an indication of the attainment of a steady-state hydroperoxide concentration.

Catalytic Hydroperoxide Formation

Attempts were made to eliminate the induction period observed in the uncatalyzed autoxidation of 1-methyl-2-pyrrolidinone using various homogeneous transition metal complexes,[17] such as Co(octoate)$_2$ (where octoate= 2-ethylhexanoate), Co(BPI) (where BPI= 1,3-bis(2-pyridylimino) isoindolene), and Mn(TPP)Cl (where TPP= tetraphenylporphyrin), which are known to catalyze Class IV radical chain reactions.[26,27] In all cases, the induction period was elim-

Table 2-1 N-Alkylamide Hydroperoxide Formation in Other Solvents.

NMP/H_2O (V/V,%/%)	[ROOH] (M)	NMP/CH_3CN (V/V,%/%)	[ROOH] (M)
100/0	1.33		
90/10	1.00	90/10	1.12
50/50	0.01	50/50	0.46
10/90	0.00	10/90	0.06

Note: Reaction conditions: 50 psig of O_2; 75°C; 50mL total solution volume.
Reaction time: 72 hours.

inated, but extensive decomposition of the N-alkylamide hydroperoxide to N-methylsuccinimide was observed.

Additional attempts focused on metal ion exchanged zeolites, such as CoNa-Y, FeNa-Y, and MnNa-Y. When the heterogeneous catalyst, CoNa-Y, is used to oxidize 1-methyl-2-pyrrolidinone, the reaction occurs as a faster rate and to a greater extent than observed for the uncatalyzed reaction.[17] The 24 hour induction period observed for the uncatalyzed reaction of this heterocyclic amide is eliminated with minimal hydroperoxide decomposition occurring.

A comparison of hydroperoxide formation with and without metal-ion exchanged zeolite catalysts is shown (Table 2-2). In contrast to CoNa-Y, Na-Y decreases the amount of hydroperoxide formed in solution. This result shows that Co(II), with its hindered accessibility, plays the key role in catalyzing hydroperoxide formation. Other metal-ion exchanged zeolites, such as FeNa-Y or MnNa-Y, also eliminate the induction period and catalyze the reaction increasing the hydroperoxide concentration relative to the uncatalyzed reaction.

4-Butyrolactone and Isopropyl Alcohol Oxidations

Several other potential hydroperoxide-forming substrates were evaluated using the CoNa-Y catalyst. When reacted with molecular oxygen (50 psig) at 75°C, both the uncatalyzed and the CoNa-Y-catalyzed autoxidations of 4-butyrolactone and isopropyl alcohol exhibited no alkyl hydroperoxide formation.

Table 2-2 Heterogeneous 1-Methyl-2-pyrrolidinone Oxidation.

Hydroperoxide Concentration (M)					
Time (hrs)	Blank	Na-Y	CoNa-Y	FeNa-Y	MnNa-Y
0	0.00	0.00	0.00	0.00	0.00
6	0.05	0.08	0.50	0.72	0.25
12	0.10	0.11	1.62	1.15	0.66
24	0.18	0.20	2.07	1.35	1.56
48	1.20	0.42	2.30	1.92	2.97
72	1.33	0.50	2.35	2.14	3.00

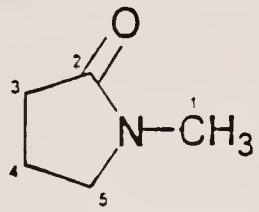
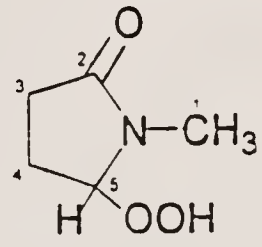
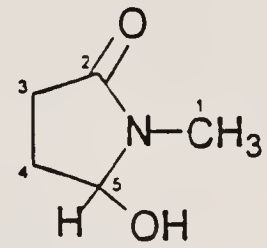
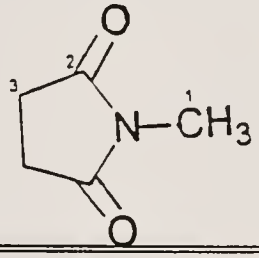
Note: Reaction conditions: 50 psig of O_2; 75°C; 50 mL of NMP. In all cases except FeNa-Y, 0.25 g of catalyst were employed. With FeNa-Y, 0.38 g.

After 120 hours of reaction, the ^{1}H NMR spectra of the reaction solutions showed no oxidation products. These compounds appear to be resistant to oxidation under the conditions employed in these reactions.

Hydroperoxide Decomposition and Oxygen Atom Transfer Ability

The decomposition and reaction of 5-hydroperoxo-1-methyl-2-pyrrolidinone with various substrates results in the formation of N-methylsuccinimide.[17,21] The amido-alcohol, 5-hydroxy-1-methyl-2-pyrrolidinone, is expected to form in the first step of an oxygen atom transfer from 5-hydroperoxo-1-methyl-2-pyrrolidinone (Figure 2-5, path (b)).[24] N-methylsuccinimide is proposed to form as a result of the facile oxidation of the amido-alcohol. To test this proposal, a pre-generated solution of 5-hydroperoxo-1-methyl-2-pyrrolidinone in 1-methyl-2-pyrrolidinone was reacted with an equimolar amount of triphenylphosphine under an inert atmosphere at $0^{o}C$ for 6 hours. A quantitative yield of triphenylphosphine oxide is produced as shown by ^{31}P NMR. The ^{13}C NMR spectrum of the solution after reaction showed resonances due to the solvent, 1-methyl-2-pyrrolidinone, and the triphenylphosphine oxide, as well as five new peaks for the amido-alcohol, 5-hydroxy-1-methyl-2-pyrrolidinone (Table 2-3). No ^{13}C resonances were detected in the solution for either the hydroperoxide, 5-hydroperoxo-1-methyl-2-pyrrolidinone, or N-methylsuccinimide.

Table 2-3 ^{13}C NMR Study of Triphenylphosphine Oxidation.

Compound	Carbon	δ(ppm)
	1	28.6
	2	173.6
	3	30.3
	4	17.4
	5	48.6
	1	26.8
	2	174.6
	3	29.6
	4	23.1
	5	94.2
	1	26.0
	2	173.1
	3	28.2
	4	27.8
	5	83.8
	1	24.2
	2	177.5
	3	28.1

Note: Resonances for $OPPh_3$ were also observed.

Exposure of the solution containing the amido-alcohol intermediate to molecular oxygen at room temperature for 24 hours results in the further oxidation of 5-hydroxy-1-methyl-2-pyrrolidinone to N-methylsuccinimide (Figure 2-5, path (b)).

The combined results of the ^{13}C and ^{31}P NMR studies of this reaction indicate that oxygen atom transfer occurs with this hydroperoxide via nucleophilic attack on the peroxide. In the absence of molecular oxygen, 5-hydroxy-1-methyl-2-pyrrolidinone results. In the presence of molecular oxygen, this product is not observed, for it is oxidized to N-methylsuccinimide by molecular oxygen under the reaction conditions.

Reduction of N-methylsuccinimide

The utility of 5-hydroperoxo-1-methyl-2-pyrrolidinone for the catalytic oxidation of organic substrates would be enhanced by the regeneration of the 1-methyl-2-pyrrolidinone from the hydroperoxide decomposition product, N-methylsuccinimide (Figure 2-5).[24] This would provide a recyclable hydroperoxide precursor with the 1-methyl-2-pyrrolidinone becoming a co-catalyst for a net reaction utilizing molecular hydrogen and oxygen. Several homogeneous methods for this stage of the catalytic cycle were studied. Since there are no literature reports on the homogeneous reduction of N-methylsuccinimide with molecular hydrogen, our initial work involved this system.

The selective reduction of carbonyl functionalities in several heterolytic compounds to methylene groups is reported in the literature. The catalyst, $RuCl_2(PPh_3)_3$, was reported by Lyons to hydrogenate succinic anhydride to 4-butyrolactone with molecular hydrogen under mild conditions.[28,29] Using this catalyst, several unsuccessful attempts were made to reduce N-methylsuccinimide to 1-methyl-2-pyrrolidinone in different solvents (Table 2-4). The addition of triethylamine to these reactions did not improve matters. Reports of the use of Ru catalysts in the hydrogenation of ketones prompted an investigation of other Ru complexes and/or solvent variations.[30-32] As seen in Table 2-4, the activities of the catalysts appear to be solvent dependent and in some cases, show high selectivities to 1-methyl-2-pyrrolidinone, but with low yields.

The hydrogenation of succinimide to the corresponding amide, 2-pyrrolidinone, has been reported in the presence of ammonia using various metal catalysts supported on carbon or silica gel.[22] The reduction of succinimide to the corresponding cyclic amide using a supported Pd catalyst and molecular hydrogen in aqueous solution is also described.[23] All of the reported hydrogenations were run under higher pressures and temperatures than employed in our experiments.

Using the catalyst, 5% Pd on activated carbon, only trace amounts of 1-methyl-2-pyrrolidinone were detected in an aqueous solution hydrogenation. This catalyst is not effective for ketone hydrogenations.[32] Of the three

Table 2-4 N-Methylsuccinimide Reduction.

Catalyst	Solvent (mL)	Products (%)
$RuCl_2(PPh_3)_3$	Toluene (5.0)	0
$RuCl_2(PPh_3)_3$ (w/ Et_3N)	Toluene (5.0)	0
$RuCl_2(PPh_3)_3$	1,4-Dioxane (5.0)	0
$RuCl_2(PPh_3)_3$ (w/ Et_3N)	1,4-Dioxane (5.0)	0
$RuCl_3 \cdot 3H_2O$	H_2O (100)	NMP (21)
$RuCl_3 \cdot 3H_2O$	Toluene/EtOH (50/50, 10)	0
cis-$RuCl_2(dmso)_4$	Toluene/EtOH (50/50, 10)	NMP (23)
cis-$RuCl_2(dmso)_4$	EtOH (10)	NMP (8)
$[Ru(dmp)_2(H_2O)_2][PF_6]_2$	Toluene/EtOH (50/50, 10)	NMPD (<1) NMP (28)
$[Ru(dmp)_2(H_2O)_2][PF_6]_2$	H_2O (100)	0
5% Pd on C	H_2O (100)	NMP (<1)
5% Ru on SG	H_2O (100)	NMP (36)
5% Ru on C	H_2O (100)	NMP (57)
5% Ru on C	H_2O (100)	NMP(>99)

Note: The above runs were performed under 100 psig of H_2 at 100°C. In the first four systems listed the amounts of substrate used was 8.8×10^{-3} moles; 4.4×10^{-5} moles of catalyst is added; and when added 4.4×10^{-4} moles of triethylamine.
In the next six systems, the amount of substrate used was 4.0×10^{-3} moles and the amount of catalyst was 4.0×10^{-5} moles. Reactions were followed for 24 hours.
In the last four reactions, the amount of substrate used was 4.0×10^{-3} moles. The amount of catalyst and reaction times were:

5% Pd on C (0.30 g), 24 hours.
5% Ru on SG (0.59 g), 72 hours.
5% Ru on C (0.30 g), 24 hours and 48 hours.

commercially available catalysts investigated, 5% Ru on carbon showed the highest yield of the corresponding cyclic amide, 1-methyl-2-pyrrolidinone (Table 2-4). In both of the Ru-catalyzed reactions, a high selectivity to the formation of 1-methyl-2-pyrrolidinone was observed.

Experimental

Reagents and Equipment

The 1-methyl-2-pyrrolidinone (HPLC grade), N-methyl-succinimide, and triphenylphosphine were obtained from Aldrich Chemical Company and used as received. $RuCl_2(PPh_3)_3$ was obtained from Strem Chemicals. All other reagents and solvents were obtained from Fischer Scientific and were used as received.

^1H and ^{13}C NMR spectra were run on a General Electric QE-300 Fourier Transform Spectrometer operated at 300 MHz and 75 MHz, respectively. The samples were run in d_6-benzene or d_1-chloroform with tetramethylsilane as an internal reference. ^{31}P NMR spectra were run on a Varian VXR 300 Fourier Transform Spectrometer operated at 121 MHz. The samples were run in d_6-benzene using H_3PO_4 (85%) as an external reference.

A Varian 3700 GC with an FID and a Hewlett Packard 3390A integrator was used to analyze the oxidation and reduction reactions, using the appropriate column for the type of compound(s) to be detected. The substrate(s) and product(s) were identified and quantified, using known standards.

Unless otherwise indicated, all reactions were run in a Parr Pressure Apparatus at the indicated temperature and pressure. CAUTION! Extreme care should be taken when working with a pressurized apparatus at or above room temperature. Appropriate shields must be used and fire extinguishers should be nearby. For elevated temperatures, the reaction solution should be cooled to room temperature before disassembling the pressure apparatus.

Peroxide concentrations were measured by taking 0.5-2.0 mL samples from the pressure bottles with a 12 in. stainless steel needle and immediately performing iodometric titrations.[33]

CAUTION! Many hydroperoxides are shock/temperature sensitive and the hydroperoxide derived from 1-methyl-2-pyrrolidinone should be treated as potentially explosive.

The catalysts, cis-$RuCl_2$ $(dmso)_4$[34,35] and $[Ru(dmp)_2(H_2O)_2][PF_6]_2$,[36] were prepared by literature methods.

Steady-State [ROOH] Studies

1-Methyl-2-pyrrolidinone (50mL, 47g, $4.7x10^{-1}$ moles) was placed in a 250 mL Parr Pressure Bottle equipped with magnetic stirring. After the pressure apparatus was assembled, the reactor was purged 3 times with O_2 (50psig) and then pressurized with O_2 (50psig). The reactor was placed in a 75°C oil bath. Recharging of the reactor with O_2 was performed as needed. Samples were periodically analyzed by ^1H and ^{13}C NMR, and iodometric titrations.

Hydroperoxide Formation in Other Solvents

The appropriate amounts (see Table 2-1) of 1-methyl-2-pyrrolidinone and the solvent (H_2O or CH_3CN) were placed in a 250mL Parr Pressure Bottle equipped with magnetic stirring. After the pressure apparatus was assembled, the reactor was 3 times with O_2 (50psig) and then pressurized with O_2 (50psig). The reactor was placed in a 75°C oil bath. Recharging of the reactor with O_2 was performed as needed. Samples were drawn periodically and analyzed by iodometric titrations.

Hydroperoxide Stability Comparison

A solution of 5-hydroperoxo-1-methyl-2-pyrrolidinone was prepared by the reaction of 1-methyl-2-pyrrolidinone with O_2 (50psig) at 75°C. The hydroperoxide concentration was determined by iodometric titration. The stability of this hydroperoxide solution was compared iodometrically with a t-butyl hydroperoxide solution of comparable hydroperoxide concentration under ambient conditions.

PPh_3 Oxidations

5-Hydroperoxo-1-methyl-2-pyrrolidinone (15mL of a 1.0M solution in 1-methyl-2-pyrrolidinone, $1.5x10^{-2}$ moles) and PPh_3 (4.0g, $1.5x10^{-2}$ moles) were placed in a 100mL round bottom flask euipped with magnetic stirring, an N_2 atmosphere, and an ice bath. After several minutes of continuous stirring at 0°C, a colorless solution resulted. The reaction solution was

stirred at 0°C for 6 hours. At that time, the colorless solution was allowed to warm up slowly to room temperature. The reaction solution was analyzed by ^{13}C and ^{31}P NMR.

Preparation of MNa-Y(M=Co^{2+}, Fe^{3+}, or Mn^{2+})

These heterogeneous catalysts were prepared by placing the appropriate chloride salt ($2.0x10^{-2}$ moles) and distilled H_2O (200mL) in a 500mL Erlenmeyer flask equipped with magnetic stirring. Na-Y (10g, Linde LZY-52) was added to the aqueous metal-ion solution. The resulting reaction slurry was stirred at 70°C (for M=Co^{2+}) or room temperature (for M=Fe^{3+} or Mn^{2+}) for 24 hours. After the cation exchange, the slurry was filtered and washed with distilled H_2O until no chloride ions were detected by $AgNO_3$ testing of the filtrates. The solid catalyst was dried under vacuum at 150°C for 48 hours. After cooling to room temperature under vacuum, the catalyst was ready for use.

Catalytic Hydroperoxide Formation

1-methyl-2-pyrrolidinone (50mL, 47g, $4.7x10^{-1}$ moles) and MNa-Y(M=Co^{2+} or Mn^{2+}, 0.25g; M=Fe^{3+}, 0.38g) were placed in a 250mL Parr Pressure Bottle equipped with magnetic stirring. After the pressure apparatus was assembled, the reactor was purged 3 times with O_2 (50psig) and then pressurized with O_2 (50psig). The reactor was placed in a 75°C oil bath. Recharging of the reactor with O_2 (50psig) was performed as

needed. Samples were drawn periodically, filtered, and analyzed by iodometric titrations.

4-Butyrolactone and Isopropyl Alcohol Oxidations

The appropriate substrate (50 mL) and CoNa-Y (0.25g, if added) were placed in a 250 mL Parr Pressure Bottle equipped with magnetic stirring. After the pressure apparatus was assembled, the reactor was purged 3 times with O_2 (50 psig) and then pressurized with O_2 (50 psig). The reactor was placed in a 75°C oil bath. Recharging of the reactor with O_2 (50 psig) was performed as needed. Samples were drawn periodically, filtered, and analyzed by ^1H NMR and iodometric titrations.

N-methylsuccinimide Reductions

The appropriate catalysts, substrate, and solvent(s) (see Table 2-4) were placed in a 250mL Parr Pressure Bottle equipped with magnetic stirring. After the pressure apparatus was assembled, the reactor was purged 3 times with H_2 (100psig) and then pressurized with H_2 (100psig). The reactor was placed in a 100°C oil bath. Recharging of the reactor with H_2 (100psig) was performed as needed. Samples were analyzed by GC using a 6 foot stainless steel column packed with FFAP(15%) on Chromosorb WA/W(80/100 mesh).

Conclusions

This research has shown that approximate 2M solutions of the N-alkylamide hydroperoxide, 5-hydroperoxo-1-methyl-2-pyrrolidinone, can be easily generated under mild conditions. This provides a convenient and inexpensive source of hydroperoxide for the oxidation of organic substrates, the initiation of radical reactions, and a variety of bleaching applications.

Having a stability comparable to the stability of the commercially-available t-butyl hydroperoxide, 5-hydroperoxo-1-methyl-2-pyrrolidinone can be produced by the direct reaction of 1-methyl-2-pyrrolidinone with molecular oxygen at 75°C. When reacted with an organic substrate, such as triphenylphosphine, the oxygen atom transfer from the hydroperoxide to the phosphine produces the amido-alcohol intermediate, 5-hydroxy-1-methyl-2-pyrrolidinone, and a quantitative yield of the corresponding phosphine oxide. In the presence of molecular oxygen, the amido-alcohol intermediate undergoes rapid oxidation to N-methylsuccinimide. Using the appropriate transition metal catalyst, N-methylsuccinimide can be hydrogenated under mild conditions to yield the hydroperoxide precursor, 1-methyl-2-pyrrolidinone. For applications in which 5-hydroperoxo-1-methyl-2-pyrrolidinone is a reactant, this recyclable nature makes 1-methyl-2-pyrrolidinone a co-catalyst for the substrate

oxidation reaction with the net reaction being

$$4H_2 + 1.5O_2 + S \longrightarrow SO + 2H_2O.$$

Another point of interest in this research is the potential application of this N-alkylamide hydroperoxide to the asymmetric oxidations of organic substrates. For example, the oxidation of alkenes by a chiral alkyl hydroperoxide and a non-chiral transition metal complex may duplicate the results observed by Sharpless and co-workers without the problems caused by unstable chiral transition metal complexes.[33]

Further suggested work in this area of regenerable alkyl hydroperoxides would involve a more in depth study into another N-alkylamide hydroperoxide precursor, 1,5-dimethyl-2-pyrrolidinone, which has been shown to form the corresponding hydroperoxide, 5-hydroperoxo-1,5-dimethyl-2-pyrrolidinone. This hydroperoxide should decompose to the corresponding amido-alcohol, 5-hydroxy-1,5-dimethyl-2-pyrrolidinone. This potential regenerable hydroperoxide system would provide for a more efficient use of molecular oxygen in the oxidative step, and a more efficient use of molecular hydrogen in the subsequent hydrogenation step. Here again, the potential for asymmetric applications exists as well.

CHAPTER 3
TRANSITION METAL-CATALYZED OXIDATIONS USING AN N-ALKYLAMIDE HYDROPEROXIDE

Introduction

The interest in the direct oxidation of alkenes to epoxides with transition metal complexes has remained very high during the years, since these compounds are key industrial intermediates for the preparation of a wide variety of chemicals, such as alkanolamines, glycols, and polymers like polyesters, polyurethanes and epoxy resins.[37] The vapor phase epoxidation of alkenes with a carbon chain length of three or more has always been difficult with low epoxide yields being obtained. For example, the oxidation of propylene with molecular oxygen over bismuth molybdate at 460°C afforded a high selectivity to acrolein.[38-40] In the presence of ammonia, this catalyst promotes the ammoxidation of propylene to acrylonitrile.[41-43]

Currently, the industrial method for making propylene oxide is based on organic hydroperoxides. The Arco Oxirane (or Halcon) process is used for the oxidation of propylene in solution.[44-46] In this process, the alkyl hydroperoxides, t-butyl hydroperoxide and ethylbenzene hydroperoxide, are prepared by the autoxidation of isobutane and ethylbenzene,

respectively. These alkyl hydroperoxides are prepared in a separate step under air or molecular oxygen (150 psig) at around 140°C. In the presence of the appropriate epoxidation catalyst, the pre-generated alkyl hydroperoxide is reacted with an excess of the olefinic substrate at 90°C to produce the epoxide. The feasibility of the Arco Oxirane process is dependent on the demand for the co-product alcohols.[47] Another advantage for this process is the attainment of high selectivities and yields.

In the Arco Oxirane process, the selectivity to epoxide formation was greatly enhanced by the choice of metal complex. When various rhenium complexes were employed, a 100% conversion of the alkyl hydroperoxide was observed with only a 10% efficiency for the formation of epoxide. Molybdenum and tungsten complexes converted 80 to 90% of the alkyl hydroperoxide with a 65 to 71% efficiency for the formation of propylene oxide. Vanadium complexes have been employed in these olefinic oxidations as well. The use of molybdenum, tungsten, and vanadium complexes generally result in higher epoxide yields. When the oxidant is H_2O_2, the tungsten complexes are the best catalysts. The molybdenum and vanadium complexes are more effective when alkyl hydroperoxides are used as the oxidant.[45]

Sheldon and Kochi conveniently designated metal-catalyzed oxidations of organic substrates as either homolytic or heterolytic.[1] The main characteristics of these two types of metal-catalyzed oxidations are summarized in Table 3-1.[48] It

Table 3-1 Main Characteristics of Homolytic and Heterolytic Oxidations.[48]

Homolytic oxidations	Heterolytic oxidations
Characteristics	
Free-radical intermediates. Outer-sphere oxidations in bimolecular steps. The substrate is generally not coordinated. Oxidations generally not very selective and not stereospecific. One-electron oxidation and reduction step of the metal.	No free-radical intermediates. The reaction occurs in the coordination sphere of the metal. The substrate is generally activated by coordination. High selectivity and stereospecificity of the transformation. No change in the oxidation state of the metal or two-electron steps.
Transition metals commonly involved.	
V^{V}/V^{IV}, Cr^{VI}/Cr^{V}, Mn^{III}/Mn^{II}, Fe^{III}/Fe^{II}, Co^{III}/Co^{II}, Cu^{II}/Cu^{I}	Ti^{V}, V^{V}, Cr^{VI}, Mo^{VI}, W^{VI}, Mn^{VII}, Ru^{VII}, $Os^{VI-VIII}$, Rh^{III}/Rh^{I}, Ir^{III}/Ir^{I}, Pd^{II}/Pd^{0}, Pt^{II}/Pt^{0}
Relevant oxidations	
Nonstereoselective epoxidations of alkenes (V,Mn,Fe). Hydroxylation of alkanes and arenes (V,Cr,Fe,Co,Cu).	Stereoselective epoxidations of alkenes (Ti,V,Mo,W). Ketonization of alkenes (Rh,Ir,Pd,Pt).

should be noted that this classification is not rigorous and there are a number of borderline examples and exceptions. Even though they are homolytic in nature, many enzymatic oxygenases containing first-row metals (e.g. Cu, Fe) as active centers function in a very high regio- and stereoselective manner. In this case, the role of the protein cage around the active center is essential for the substrate-enzyme association and the right orientation of the substrate toward the active center. In other cases, the free-radical intermediates can remain close to the metal and react in a concerted way before inversion. There are several examples where the metal complex can act as both a homolytic and heterolytic catalyst. Using alkyl hydroperoxides, vanadium complexes stereoselectively epoxidize allylic alcohols via vanadium (V) alkylperoxo intermediates.[49] However, vanadium (V) alkylperoxo complexes, such as V(O)(dipic)(OOR)L (where dipic=2,6-pyridinedicarboxylate and L=H_2O), react homolytically as a result of the lack of an available coordination site for the complexation of the olefinic substrate to occur.[50] In general, the homolytic and heterolytic nature of the oxidation is determined by the nature of the metal, the nature of the ligands, the availability of coordination sites, the nature of the substrate, and the temperature conditions.[48]

Recently, Drago developed a more detailed classification scheme for homogeneous metal-catalyzed oxidations of organic substrates where the reactions are grouped into classes based

on the role of the transition metal complex.[26,27] This classification scheme consists of five different classes (Table 3-2).

Class I reactions involve the coordination of molecular oxygen to the transition metal complex as described by the spin pairing model[51]; thereby, increasing both the basicity and the radical reactivity of the O_2 molecule. The subsequent oxidation of the substrate occurs via reaction with the coordinated O_2 molecule.

The reaction of a transition metal complex with molecular oxygen can result in the formation of a high-valent metal oxo species, which efficiently uses both oxygen atoms of the O_2 molecule to oxidize the substrate. This Class II behavior is indicative of dioxygenate catalysts.[26,27] Subsequent oxygen atom transfer or other type reactions in the oxidation of the organic substrate by the high-valent metal oxo complex results in the regeneration of the lower oxidation state of the metal; thus, allowing for the reformation of the high-valent metal oxo species from molecular oxygen.

Class III reactions involve the generation of a metal oxo species by reducing molecular oxygen to peroxo complexes, alkylperoxo complexes, H_2O_2, or alkyl hydroperoxides.[26,27] Oxidation of the substrate occurs via the reaction of the high-valent metal oxo species with the substrate. For most of these reactions, only one of the oxygen atoms of the O_2 molecule is utilized in the oxidation of the substrate. These

Table 3-2 Classification Scheme for Metal-Catalyzed Oxidations.[26,27]

Class	Role of Metal
I	Metal-bound O_2.
II	Metal oxo via O_2.
III	Metal oxo via peroxides.
IV	Metal peroxo systems.
(a)	Metal-catalyzed peroxide decomposition.
(b)	Nucleophilic attack on peroxo and alkylperoxo complexes.
(c)	Other reactions of metal peroxo complexes.
V	Metal-centered oxidizing agents.

reactions often exhibit monooxygenate behavior but, in some cases, dioxygenate behavior can occur.

Work by Drago and Goldstein has shown that the complex, $[Ru(dmp)_2(H_2O)_2]\ [PF_6]_2$ is oxidized to metal oxo complexes through the Ru(III) to the Ru(IV) and Ru(VI) oxidation states by alkyl hydroperoxides generated during the induction period in the oxidation of alkenes.[52] Reaction between the substrate and the Ru(VI) dioxo species results in the formation of the Ru(IV) mono oxo complex which can be reoxidized back to the Ru(VI) dioxo species with molecular oxygen. This transition metal complex exhibits Class III reactivity with alkyl hydroperoxides to form the Ru(IV) mono oxo species, followed by a Class II reaction to form the Ru(VI) dioxo complex with molecular oxygen.

Unlike the Class II and Class III reactions, which involve high-valent metal oxo complexes as reactive intermediates, Class IV reactions involve alkylperoxo and hydroperoxo transition metal complexes as intermediates.[26,27] These metal peroxo complexes exhibit three types of reactivity in the oxidation of the substrate, resulting in three subclasses of this class of reactions. The first subclass, Class IVa, deals with the transition metal-catalyzed decomposition of hydroperoxides (Haber-Weiss and Fenton chemistry). According to the Haber-Weiss mechanism, the homolytic decomposition of alkyl hydroperoxides by transition metal ions generates alkoxy- and alkylperoxy-radicals which initiate free-radical chain reactions (Figure 3-1).[53-55]

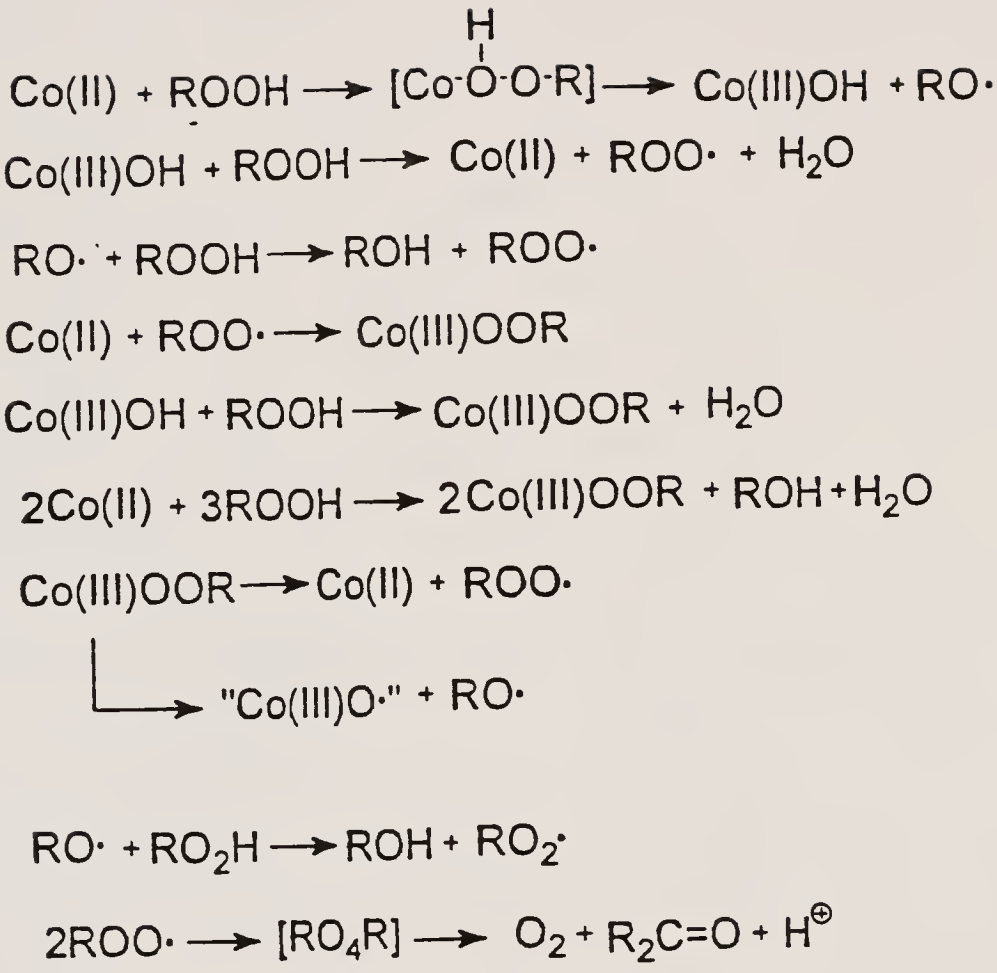

H
Co(II) + ROOH → [Co-O-O-R] → Co(III)OH + RO·
Co(III)OH + ROOH → Co(II) + ROO· + H2O
RO· + ROOH → ROH + ROO·
Co(II) + ROO· → Co(III)OOR
Co(III)OH + ROOH → Co(III)OOR + H2O
2Co(II) + 3ROOH → 2Co(III)OOR + ROH + H2O
Co(III)OOR → Co(II) + ROO·
"Co(III)O·" + RO·
RO· + RO2H → ROH + RO2·
2ROO· → [RO4R] → O2 + R2C=O + H⊕

Figure 3-1 Haber-Weiss Mechanism for Decomposition of Alkyl Hydroperoxides.[26,27]

Budnik and Kochi reported the cobalt-catalyzed epoxidation of several olefins using molecular oxygen and t-butyl hydroperoxide.[56,57] The mechanism proposed for the olefin epoxidations using molecular oxygen involves an initiation reaction between $Co(acac)_3$ and molecular oxygen to produce free-radicals.[56] The subsequent reaction of these free-radicals with molecular oxygen results in peroxy-radical formation. Addition of the peroxy-radical to the olefinic bond leads to a β-peroxyalkyl radical intermediate, which undergoes fragmentation to give the epoxide and carbonyl compounds. Using t-butyl hydroperoxide as the oxidant in the Cobalt(II)-catalyzed epoxidation of olefins, Kochi proposed a radical-chain mechanism in which the homolytic addition of t-butylperoxy-radicals to the olefinic bond leads to epoxide formation (Figure 3-2).[57] The cobalt catalysis is associated with the Co^{II}/Co^{III} interconversion in the one-electron redox processes resulting in the formation of the t-butylperoxo-radical.

On the other hand, the transition metal-catalyzed decomposition of H_2O_2 via one-electron redox processes results in the formation of hydroxyl-radicals (Figure 3-3).[1,58,59] In the presence of organic substrates, these hydroxyl radicals produce organic free-radicals, which can undergo dimerization, oxidation, or reduction (Figure 3-3).[1] These free-radical processes lead to low yield, unselective substrate oxidations as a result of the competing non-efficient hydroperoxide decomposition.

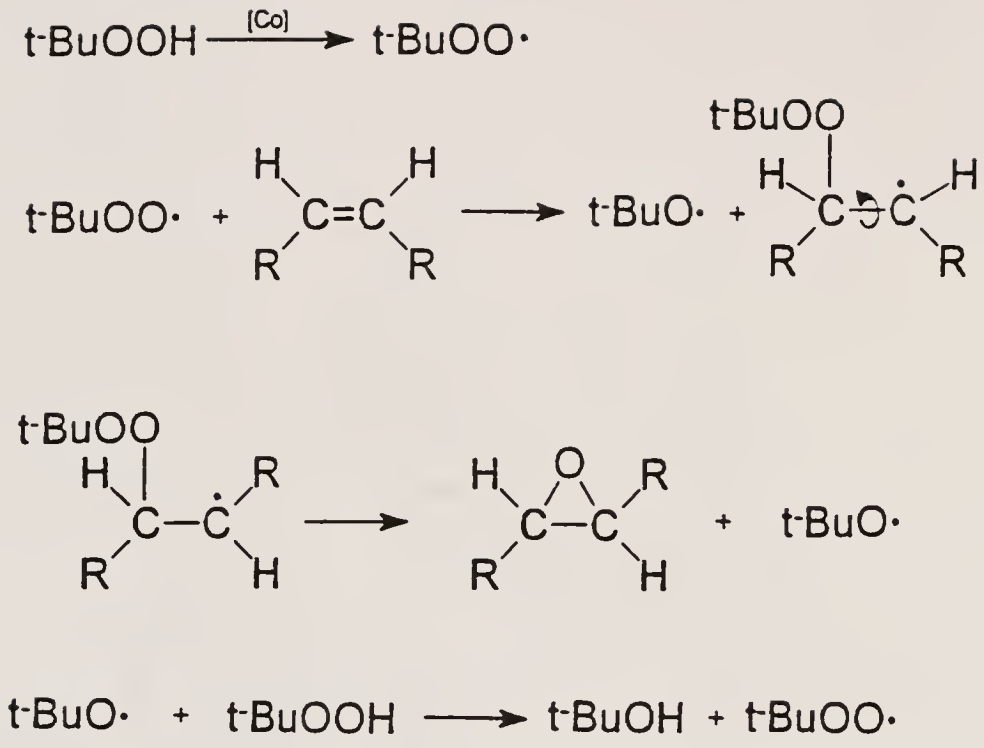


Figure 3-2 Radical-Chain Mechanism Leading to Epoxide Formation.

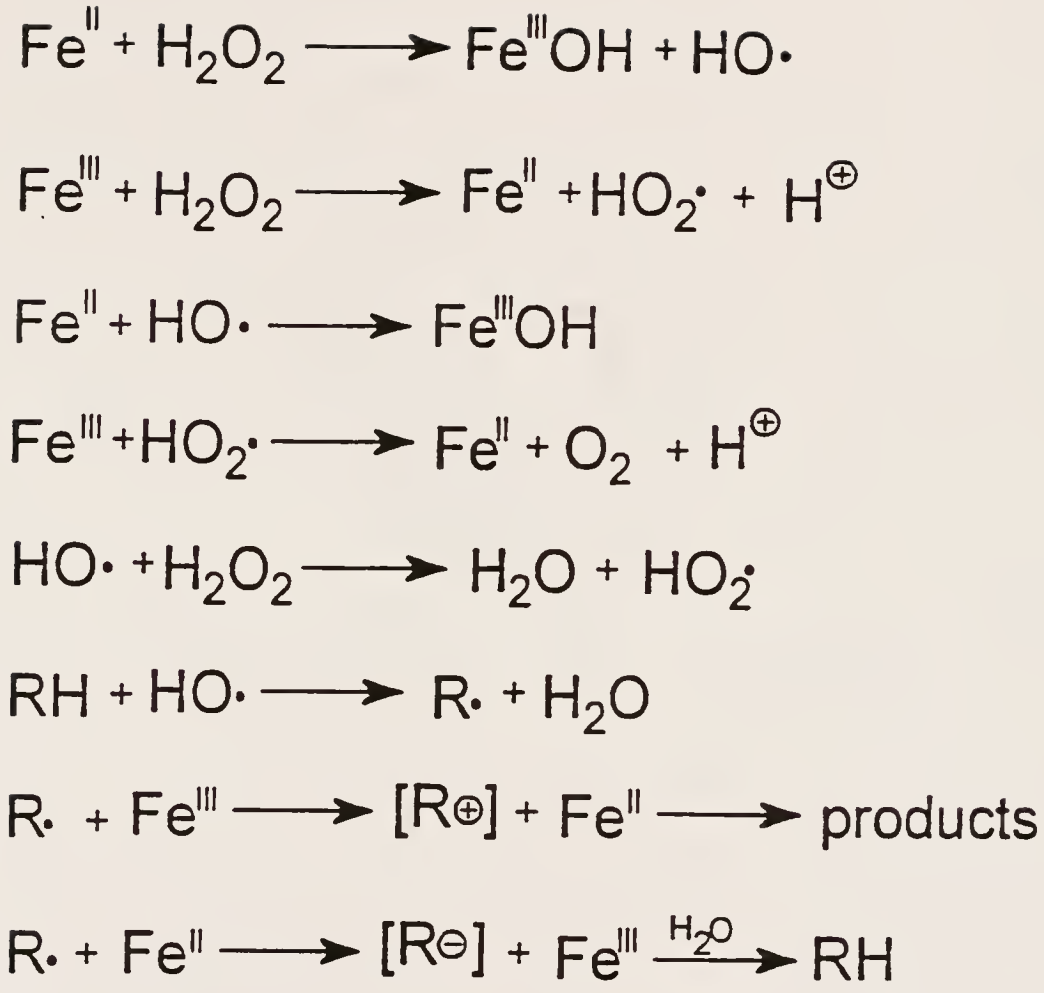

Fe^II + H2O2 → Fe^IIIOH + HO·
Fe^III + H2O2 → Fe^II + HO2· + H^⊕
Fe^II + HO· → Fe^IIIOH
Fe^III + HO2· → Fe^II + O2 + H^⊕
HO· + H2O2 → H2O + HO2·
RH + HO· → R· + H2O
R· + Fe^III → [R⊕] + Fe^II → products
R· + Fe^II → [R⊖] + Fe^III —H2O→ RH

Figure 3-3 Fenton Chemistry Mechanism.[1]

Nucleophilic attack by the substrate on a coordinated peroxo or alkylperoxo ligand can be described as a Class IVb reaction.[26,27] As noted earlier, these heterolytic reactions exhibit a high degree of product selectivity (Table 3-1). Two mechanisms for this class of metal-catalyzed olefin epoxidations have been proposed by Mimoun,[60] Chong and Sharpless,[61] and Sheldon.[62] The Mimoun mechanism involves a dipolar addition to form a peroxymetallocycle, which decomposes to yield the epoxide and the metal alkoxide (Figure 3-4).[60] The metal peroxo complex is regenerated with the alkyl hydroperoxide.

The mechanism proposed by Sharpless[61] and Sheldon[62] involves the nucleophilic attack of the olefin on the coordinated peroxo oxygen to give the cooresponding metal alkoxide and the epoxide (Figure 3-5). The regeneration of the metal peroxo species with alkyl hydroperoxide and its subsequent reaction with the olefin to give a metal alkoxide result with no change in the metal oxidation state.

Other reactions involving metal peroxo intermediates belong to Class IVc.[26,27] For example, the Co(SMDPT) (where SMDPT= bis(salicylidene-γ-iminopropyl)methylamine)-catalyzed reactions of olefins with molecular oxygen in reducing solvents results in the oxidation of the internal carbon of the double bond to give alcohols and ketones.[63] The mechanism suggests the formation of a metal hydroperoxo species which undergoes a Markonikov addition across the double bond of the

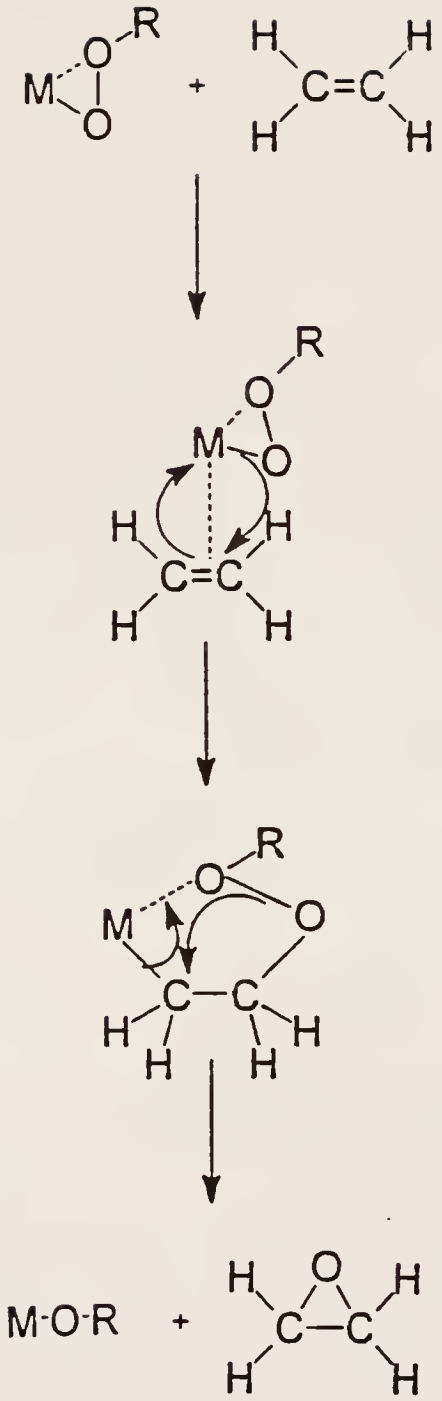


Figure 3-4 Peroxymetallocycle Mechanism.[60]

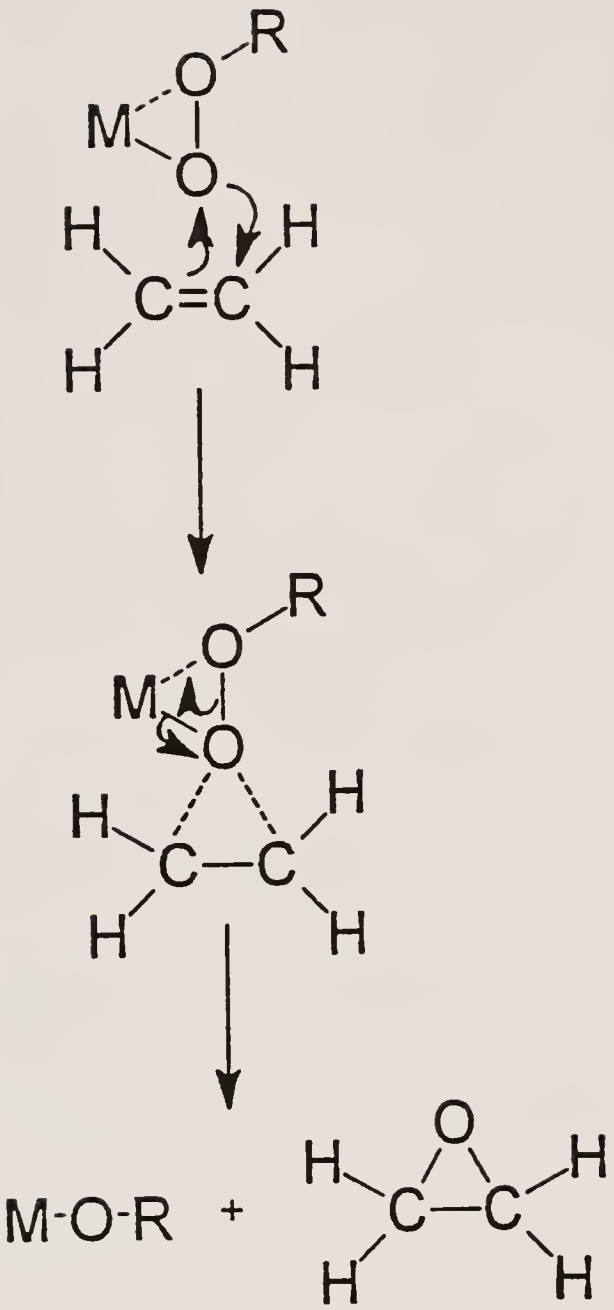


Figure 3-5 Sharpless Epoxidation Mechanism.[61,62]

olefin to form a metal alkylperoxo complex. Haber-Weiss decomposition of the alkyl hydroperoxide leads to the observed products.

Class V reactions involve the oxidation of the substrate by a high-valent metal complex, followed by reoxidation of the reduced metal complex with molecular oxygen or peroxides.[26,27] The oxidation of ethylene to acetaldehyde by the Wacker process belongs to this class.[64,65]

Since some metal catalysts play several roles in a reaction, the reaction can involve a combination of the above mentioned classes.[26,27] Other reactions discussed in this work will be described using this recent classification scheme.

As mentioned earlier, two mechanisms for the metal-catalyzed epoxidation of olefins involving Class IVb behavior have been described by Landau et al.,[47] Eberson,[66] Jonsson,[67] Parshall,[68] Mimoun,[69] and Sharpless et al.[70] Epoxidations carried out in the presence of ^{18}O-enriched H_2O by Sharpless et al. showed that the epoxide oxygen originated from the alkyl hydroperoxide.[71] The mechanism proposed by Mimoun (Figure 3-4) does not distinguish between metal peroxo oxygen atoms on the catalyst before the addition of the hydroperoxide and those added to the metal peroxo complex by the hydroperoxide. The findings by Sharpless et al. suggest a mechanism involving the transfer of one of the peroxo oxygens to the olefin through a three-membered ring transition state.[71] In subsequent literature reportings,[37,70,72] Sheldon and Sharpless described a mechanism which involved this

intermediate in the epoxidation of olefins by metal alkylperoxo complexes. The mechanism proposed by Sharpless provides a better explanation for the epoxidation of allylic alcohols with their coordinated hydroxyl groups[70] than does the Mimoun mechanism.[53,73] The isolation of several metal alkylperoxo complexes by Mimoun and co-workers has provided evidence for the elimination of mechanisms in which the alkyl peroxide binds to the metal through the oxygen atom adjacent to the alkyl group and clearly demonstrated that the isolated metal alkylperoxo complex is a selective epoxidation catalyst.[73]

In their investigation of the metal acetylacetonate-catalyzed epoxidation of olefins, Indicator and Brill observed a 100% selectivity to epoxide in the oxidation of 2,4,4-trimethyl-1-pentene using $Cr(acac)_3$, $Mo(acac)_2$, $V(O)(acac)_2$, and $V(acac)_3$.[74] These Class IVb[26,27] epoxidations are stereospecific with trans-4-methyl-2-pentene yielding the trans epoxide and cis-4-methyl-2-pentene yielding the cis-epoxide. No epoxidation of the olefins by the hydroperoxide alone was observed.

In the presence of various amines, such as pyridine, epoxides were selectively obtained from the reaction of several different aliphatic and aromatic olefins with t-butyl hydroperoxide and $Mo(O)_2(acac)_2$ in a non-polar solvent at 70°C.[75] These reactions are stereoselective with cis-olefins yielding cis-epoxides and trans-olefins yielding trans-epoxides; thus, exhibiting Class IVb character.[26,27] The

mechanism by which the added amines assist in the observed selectivity to epoxide formation was not elucidated.

The epoxidation of cyclohexene and 1-octene at 90°C using t-butyl hydroperoxide and molybdenum catalysts, $Mo(O)_2(acac)_2$ and $Mo(CO)_6$, resulted in the formation of 1,2-epoxycyclohexane (94%) and 1,2-epoxyoctane (64%), respectively.[76] These findings suggest the active catalyst should be a weak oxidant and a fairly strong Lewis acid. High-valent metal complexes (i.e. Mo(VI), Ti(IV), or W(VI)) meet these requirements.[76,77] High selectivity to the formation of epoxide was observed using cumene hydroperoxide as well.[78]

Several oxovanadium complexes have been studied as catalysts for olefin epoxidations. Compared with molybdenum catalysts, vanadium complexes have been found to be poor catalysts for olefin epoxidations.[79,80] The molybdenum(VI)-catalyzed epoxidations are about 10^2 times faster than those catalyzed by vanadium(V) complexes.[1,80] Interestingly, the epoxidation of allylic alcohols using vanadium catalysts proceeds at higher rates and at higher yields than high-valent molybdenum catalysts.[81] The dependence of the stereoselectivity of epoxidation reactions catalyzed by vanadium oxo complexes is due to the nature of the ligand present.[50,73,82] If 2,6-pyridine-dicarboxylate is present as a ligand, cis-2-butene gives a 3:1 mixture of the cooresponding cis- and trans- epoxides,[83] whereas the presence of the tridentate

Schiff base ligand, N-(2-hydroxyphenyl) salicyclideneamine, the epoxidation of cis-2-butene results in only cis-2,3-epoxybutane.[73]

Using t-butylhydroperoxide as the oxidant, ^{18}O-labeling studies of vanadium(V) oxo-catalyzed epoxidations have shown the existence of a metal peroxo intermediate and favor a vanadium(V) alkylperoxo complex as the active species.[61,84] Mimoun et al. have isolated and characterized a stable vanadium(V) oxo alkylperoxo complex possessing a triangularly bound t-butyl peroxo group and having both equatorial adjacent positions occupied by the tridentate dipicolinate ligand.[73] These vanadium(V) alkylperoxo complexes have been suggested to be the active species in the epoxidation of alkenes, with the alkylperoxo ligand coordinated in a monodentate or bidentate fashion (Figure 3-6).[79]

The transfer of the oxygen atom from vanadium alkylperoxo complexes as well as from other transition metal d^o alkylperoxo and peroxo species has received a great deal of attention.[79] Three mechanisms are shown in Figure 3-7.

In the first mechanism, the metal hydroxo alkylperoxo complex, resulting from the reaction of the vanadium oxo (or other d^o metal oxo) complex with an alkyl hydroperoxide, transfers an oxygen atom to the electron-rich olefin to give the corresponding epoxide, the starting metal oxo complex, and the alcohol derived from the alkyl hydroperoxide. This type of reactivity indicates a Class IV reaction (Figure 3-7).[26,27]

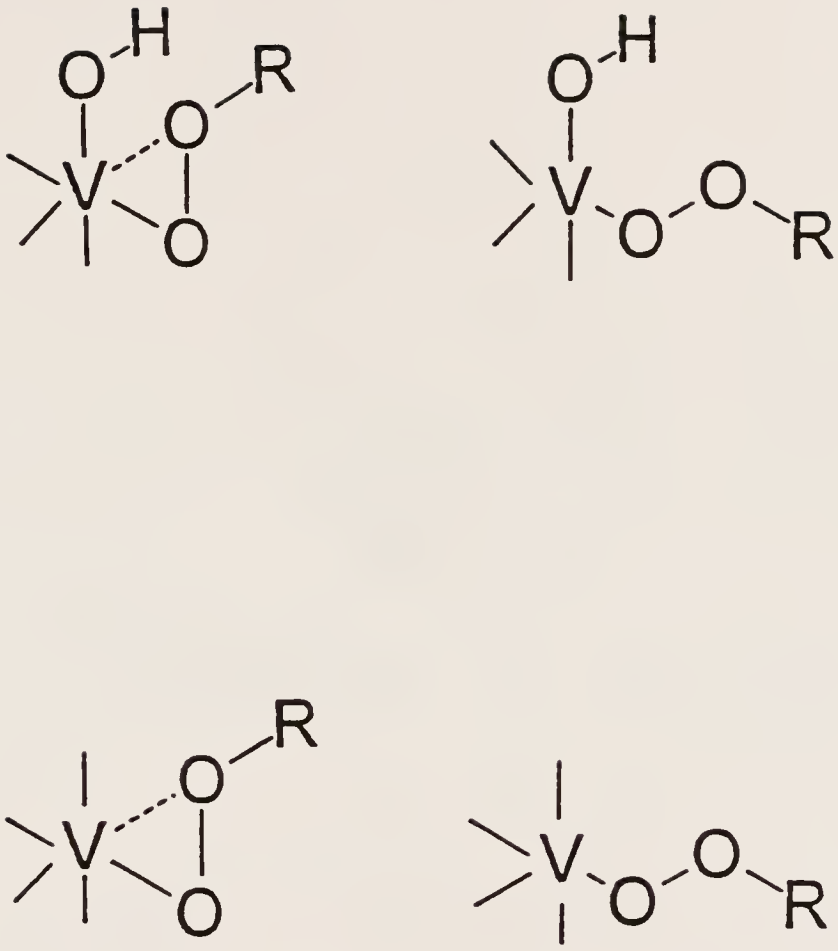


Figure 3-6 Coordination Modes for Alkylperoxo Ligands.[79]

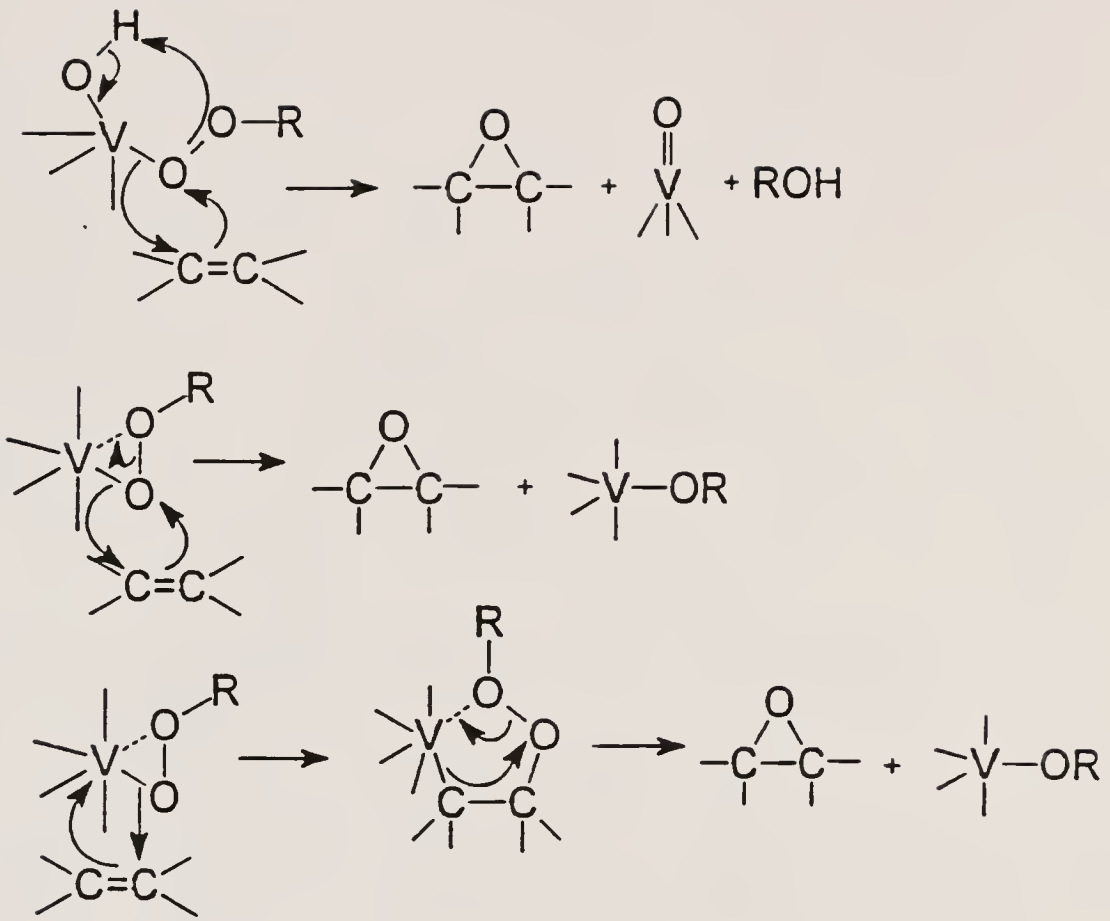


Figure 3-7 Oxygen Atom Transfer from d^o Transition Metal Alkylperoxo Complexes.[79]

The nucleophilic attack of the olefin on the coordinated peroxo oxygen of a metal alkylperoxo complex, produced by the reaction of a high-valent transition metal complex with an alkyl hydroperoxide, leads to the epoxide and a metal alkoxide (Class IV).[26,27] No change in the metal oxidation state occurs (Figure 3-7).

The third mechanism in Figure 3-7 occurs via a five-membered peroxometallocycle intermediate.[48] The first step in this mechanism involves the coordination of the alkene to the metal center, followed by insertion of the coordinated alkene into the metal-peroxygen bond to give a peroxymetallocycle intermediate. The subsequent decomposition of the peroxymetallocycle results in the formation of the epoxide and the metal alkoxide (Class IV).[26,27]

In general, vanadium complexes are less efficient and selective catalysts than molybdenum compounds for the epoxidation of unactivated olefins.[80] Mimoun and co-workers studied the heterolytic and homolytic oxygen atom transfer from stable metal alkylperoxo complexes for the stereoselective oxidation of alkenes.[53,73,82] The heterolytic (Figure 3-7) or homolytic (Figure 3-8) dissociation mode of the vanadium alkylperoxo species controls the nature of the catalytic oxidation.[82] For instance, the earlier mentioned vanadium(V) oxo alkylperoxo Schiff base complex exhibited a high degree of selectivity and stereoselectivity in the oxidation of cis-2-butene, giving cis-2,3-epoxybutane as the only product.[73] The heterolytic behavior of this catalyst is

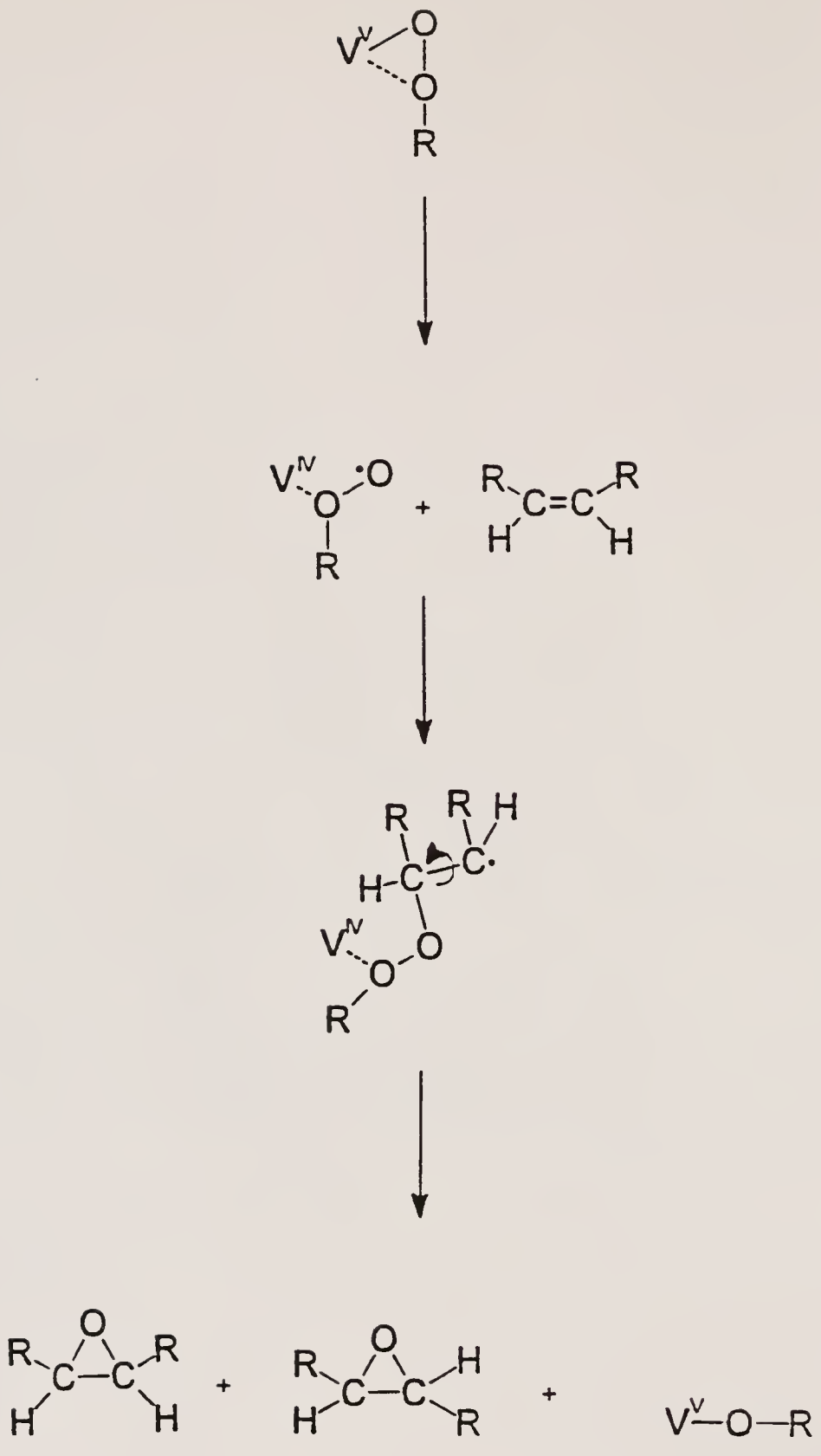


Figure 3-8 Homolytic Epoxidation Pathway for Vanadium Peroxo Complexes.[79]

indicative of Class IVb reactions.[26,27] On the other hand, the epoxidation cis- and trans-2-butene by vanadium(V) peroxo complexes resulted in mixtures of cis- and trans-epoxide of 1:2 and 1:6.[84] These non-stereoselective epoxidations are characteristic of a homolytic process, which is suggested to involve a biradical vanadium(IV) alkylperoxo species (Figure 3-8).[82] The suggested intermediate would account for the isomerization of cis alkenes to yield mixtures of cis and trans epoxides by allowing for rotation about the carbon-carbon bond.

While much work has been done on the selective and stereoselective metal-catalyzed formation of epoxides, the area of asymmetric transition metal-catalyzed epoxidations using alkyl hydroperoxides has received little attention. The catalytic asymmetric epoxidation of unfuntionalized alkenes with large enantiomeric excesses(ee) has proven to be very difficult.[85] Using t-butyl hydroperoxide as the oxidant, Otsuka and co-workers obtained a 10% ee in the epoxidation of 1-methylcyclohexane using a $Mo(O)_2(acac)_2$/DIPT catalyst.[86]

The ability of metal alkylperoxo complexes to selectively epoxidize alkenes has been increased using allylic alcohol substrates. As mentioned earlier, vanadium complexes were found to be very efficient catalysts for allylic epoxidations using t-butyl hydroperoxide.[81] In the oxidation of allylic alcohols, vanadium catalysts favor the formation of the erythro-epoxy alcohols,[87,88] while the use of m-chloroperoxybenzoic acid favors the threo-epoxy alcohols.[89]

The observed acceleration in the rate and the high regioselectivity of these reactions suggest a mechanism in which the alcohol is coordinated to the metal in the rate determining step.[81,89]

Chiral molybdenum[90] and vanadium[70] complexes have been applied in the asymmetric epoxidation of allylic alcohols. In the presence of the chiral molybdenum complex, $Mo(O)_2(acac)$ [(-)-N-alkylephedrinate], and cumene hydroperoxide, allylic alcohols were epoxidized to the corresponding optically active epoxy alcohols (maximum 33% ee).[90] The vanadium hydroxymate catalyst, generated in situ from $V(O)(acac)_2$ and chiral hydroxamic acids.[70] Enantiomeric excesses of up to 50% were observed using this catalyst, while the chiral molybdenyl bis-hydroxymate complexes exhibited poor asymmetric inductions (<2%) under analogous experimental conditions.

Probably the best known method for the asymmetric epoxidation of allylic alcohols involves the reaction of a mixture of a titanium(IV) alkoxide, an optically active tartrate ester, and t-butyl hydroperoxide with allylic alcohols to form epoxy alcohols in good yield and with enantiomeric excesses generally greater than 90% at minus 23°C.[33,91-99] Rearrangement of the epoxy alcohols to their corresponding diols results upon exposure of the epoxy alcohols to the $Ti(O^iPr)_4$ at or above room temperature.[92]

When using catalytic amounts of the titanium(IV) alkoxide and the chiral tartrate ester, the yields in the asymmetric epoxidation of allylic alcohols are generally low. Higher

yields (>95%) and high enantiomeric excesses (90-95% ee) result from the addition of 3A or 4A molecular sieves during the reaction.[33,99] The molecular sieves are thought to protect the catalyst from adventitious H_2O and H_2O that may be generated in small amounts during the reaction.

Using the Sharpless method, the kinetic resolution of racemic allylic alcohols can be performed by varying the oxidation rate.[93] At rapid rates of oxidation, the epoxidation of the (S)-enantiomer is 98% selective for the formation of the erythro enantiomer. The slower asymmetric epoxidation of the (R)-enantiomer results in a 62% selectivity for the erythro epoxy alcohol. Complexes of diisopropyl tartrate and $Ti(O^tBu)_4$ were found to catalyze the kinetic resolution of racemic, secondary allylic alcohols with low efficiencies relative to those complexes generated from $Ti(O^iPr)_4$.[100]

In order to gain some insight into the structure of the active catalytic species, the titanium-catalyzed asymmetric epoxidation of allylic alcohols were investigated using linked bis-tartrate esters as ligands.[101] The inability of the linked tartrate derived catalyst to mediate efficient kinetic resolution of the secondary allytic alcohols argues against the sole intermediacy of and against epoxidation exclusively by a momomeric titanium tartrate species. A detailed solution study of this catalytic system suggested that the asymmetric epoxidation catalyst is a dimer,[102] with the most active catalyst in the reaction mixture containing equimolar amounts

of the titanium alkoxide and the tartrate ester.[103] Titanium complexes containing the "tartrate-like" ligands, (3R, 4R)-diisopropyl-3,4-dihydroxyadipate, (2S, 4S)-diisopropyl-2,4-dihydroxyglutarate, and (2S, 5S)-diisopropyl-2,5-dihydroxy-adipate were found to be dimeric; thereby, providing further support for the active catalytic species.[104]

Metalloporphyrin complexes have been used in the selective oxidation of alkenes. The iron(II)- and manganese(II)- containing 5,10,15,20-tetraphenylporphyrins are the most commonly used metalloporphyrins for the oxidation of organic substrates. The iron(IV) porphyrins are proposed to contain the ferryl group,[105-108] which is suggested to be the active species for the epoxidation of alkenes.[109-112] The difficulty in the formation of the ferryl species with the tetraphenylporphyrin ligand results from the tendency to form the peroxy-bridged metalloporphyrin complex.[113,114] The dimerization problems associated with the metal tetraphenyl-porphyrin complex can be overcome using porphyrins containing bulkier groups,[110,111] or the addition of nitrogen bases to stabilize the monomeric species.[112]

Simple iron(III) and manganese(III) porphyrins were unable to catalyze the epoxidation of alkenes using alkyl hydroperoxides.[115,116] Mansuy and Bartoli proposed a "Fenton-like" homolytic cleavage of the alkyl hydroperoxide oxygen-oxygen bond and not a heterolytic cleavage of this bond, which would lead to the epoxidizing iron(V) oxo- or manganese(V) oxo-species.[115] In the presence of a catalytic amount of the

stabilizing base, imidazole, these iron(III)- or manganese(III)-tetraphenylporphyrin complexes catalyzed the epoxidation of several olefins using cumyl hydroperoxide.[117]

Results and Discussion

During an earlier performed solvent variation study for the metal-catalyzed oxidations of alkenes, the solvent 1-methyl-2-pyrrolidinone exhibited a high selectivity for epoxide formation in the cobalt(II)-catalyzed oxidation of 1-hexene with molecular oxygen.[17] This selectivity to epoxide would be expected for oxygen atom transfer reactions; thereby, suggesting the involvement of the solvent by chemical reaction. In a subsequent study, the direct reaction of 1-methyl-2-pyrrolidinone with molecular oxygen at 75°C was found to form the corresponding hydroperoxide, 5-hydroperoxo-1-methyl-2-pyrrolidinone, which is decomposed to N-methyl-succinimide in the presence of a peroxide decomposition catalyst.[17] This hydroperoxide quantitatively oxidized PPh_3 to $OPPh_3$ by oxygen atom transfer to give the amido-alcohol intermediate, 5-hydroxy-1-methyl-2-pyrrolidinone, which further oxidizes in the presence of molecular oxygen to N-methylsuccinimide.[24,25] Furthermore, the final decomposition product, N-methylsuccinimide, can be hydrogenated under mild conditions using various transition metal catalysts to the hydroperoxide presuror, 1-methyl-2-pyrrolidinone, to provide a catalytic cycle for the oxidation of substrates using molecular hydrogen and molecular oxygen with 1-methyl-2-

pyrrolidinone, in effect functioning as a catalyst (Figure 2-5).[24,25]

Recently, we have reported applications of this in situ generated alkyl hydroperoxide system elsewhere.[25]

Employing a recently reported classification scheme for the metal-catalyzed oxidation of organic substrates,[26,27] we present a more in depth study into the role of the transition metal catalysts in the oxidations of various substrates using this hydroperoxide in 1-methyl-2-pyrrolidinone solvent.

Cyclohexene Oxidation

Our initial investigations were performed using the cyclic olefin, cyclohexene. After 72 hours of reaction, both the metal-catalyzed and the uncatalyzed olefin oxidations in 1-methyl-2-pyrrolidinone showed a predominance of the allylic products, 2-cyclohexen-1-ol and 2-cyclohexen-1-one, which arose from the autoxidation of the substrate (Table 3-3). Looking at the results given in Table 3-3, the employment of several molybdenum epoxidation catalysts, including $Mo(O)_2(acac)_2$ (Class IVb),[26,27] display a preference to the allylic alcohol and ketone, while the catalyst, $V(O)(acac)_2$ (Class IVb)[26,27] showed a much greater preference to the allylic products. The vanadium catalyst, with its radical initiating pathway (Class IVa component),[26,27] appears to catalyze the more facile olefinic autoxidation more readily than the hydroperoxide formation. In all cases except the oxidation by $Na_2WO_4 \cdot 2H_2O$ (Class IVb), the epoxide, which

Table 3-3 Cyclohexene Oxidation.

Catalyst	Epoxide:Allylic Alcohol: Allylic Ketone Ratio
none	1.0:1.6:9.1
MoO_3	1.0:3.3:15.3
$Na_2WO_4 \cdot 2H_2O$	1.0:3.3:10.8
$Na_2MoO_4 \cdot 2H_2O$	no epoxide, only allylic products
$Mo(O)_2(acac)_2$	1.0:2.0:5.4
$V(O)(acac)_2$	1.0:11.4:27.8

Note: Reaction conditions:
catalyst (3.0×10^{-5} moles)
substrate (3.0×10^{-2} moles)
NMP (47 mL)
run under O_2 (50 psig) at 75°C for 72 hours.

results from the hydroperoxide, was not detected within the first 24 hours of the reaction. These combined observations show that there is a competition between the autoxidation of the substrate and the formation of the N-alkylamide hydroperoxide derived from 1-methyl-2-pyrrolidinone (Figure 3-9).

trans-β-Methylstyrene Oxidation

Experiments in which trans-β-methylstyrene was used as the olefinic substrate were performed (Table 3-4). It is interesting to note that the uncatalyzed oxidation showed an epoxide to benzaldehyde ratio of 2:1. Furthermore, the results in Table 3-4 show that the variation of the transition metal catalyst used has a pronounced effect on the epoxide to benzaldehyde ratio as well as the times for the complete consumption of the substrate in these reactions.

The $CoCl_2 \cdot 6H_2O$, $Co(octoate)_2$, and $Co(OAc)_2 \cdot 4H_2O$ (all three catalysts, Class IVa)[26,27] results for the oxidation of this aromatic olefin show a larger selectivity for the epoxidation of the substrate than the other catalysts listed. This seemed to be an anomaly, until a color change of the catalyst was observed during the reaction. The color change indicated that the 1-methyl-2-pyrrolidinone had probably replaced the other ligands on the cobalt metal centers. This change of ligands radically increased the selectivity of the reaction, since $Co(octoate)_2$ is an industrial free-radical catalyst for the non-selective oxidation of alkanes.[54] An attempt was made to

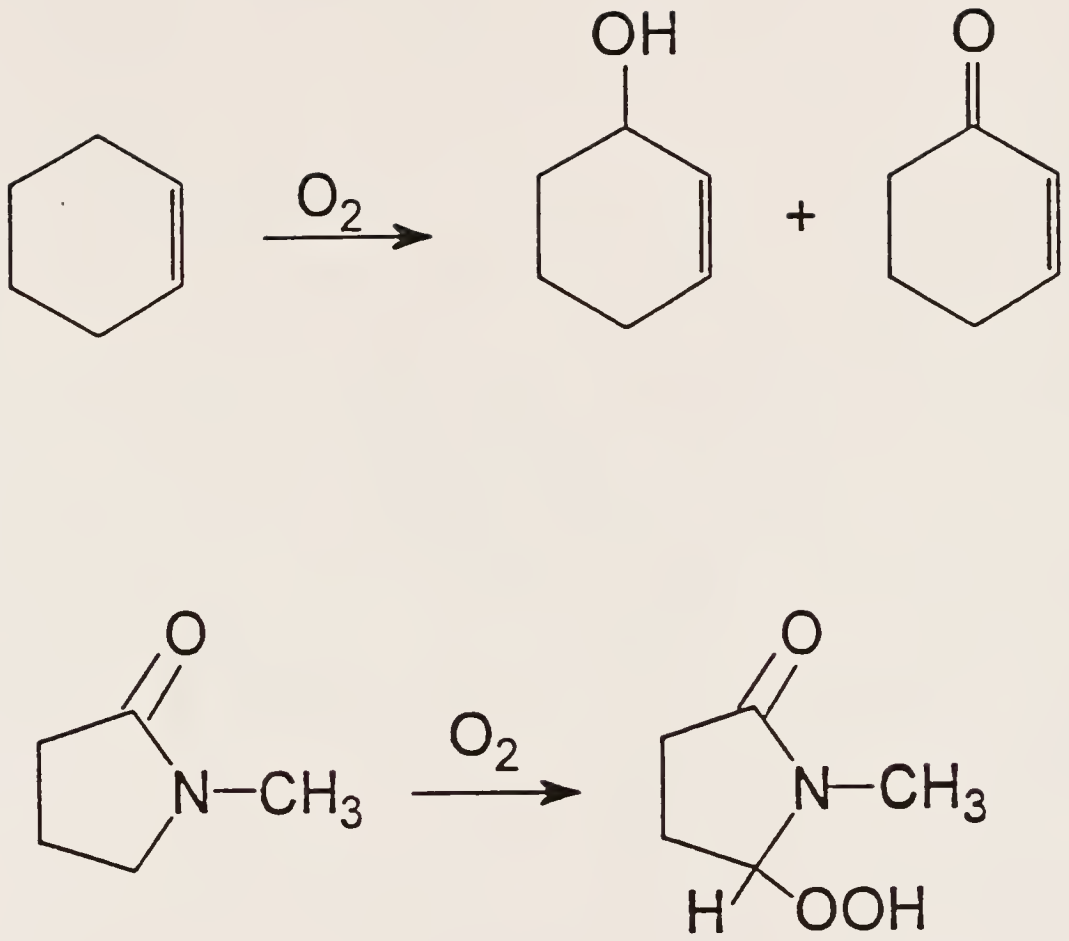


Figure 3-9 Competitive Reactions in Cyclohexene Oxidation.

Table 3-4 trans-β-Methylstyrene Oxidation.

Catalyst	Epoxide:Benzaldehyde Ratio
none	2.0:1.0 (72 hours)
$CoCl_2 \cdot 6H_2O$	6.0:1.0 (12 hours)
$Co(octoate)_2$	6.0:1.0 (18 hours)
$Co(OAc)_2 \cdot 4H_2O$	6.0:1.0 (16 hours)
$FeCl_3 \cdot 6H_2O$	4.0:1.0 (12 hours)
$[Ru_3O(pfb)_6(Et_2O)_3](pfb)$	2.3:1.0 (6 hours)
$RuCl_3 \cdot 3H_2O$	3.5:1.0 (12 hours)
$[Ru(dmp)_2(H_2O)_2][PF_6]_2$	1.0:6.0 (12 hours)
$Mn(OAc)_2 \cdot 4H_2O$	1.0:2.8 (13 hours)
$Mo(O)_2(acac)_2$	1.0:3.4 (48 hours)
$V(O)(acac)_2$	1.0:4.3 (26 hours)
WO_3	1.0:1.8 (35 hours)

Note: Reaction conditions:
catalyst (2.3×10^{-5} moles)
substrate (2.3×10^{-2} moles)
NMP (47 mL)
run under O_2 (50 psig) at 75°C.
Substrate consumption times given in parentheses.

study the cobalt(II)-catalyzed reaction of 1-methyl-2-pyrolidinone with molecular oxygen at 75°C by UV/vis spectroscopy in order to determine the nature of the species involved. Looking at the UV/vis spectra taken at various time intervals, the absorbance observed at 664 nm, which is in the Co(II) region, showed no changes over a 24 hour period, even though the solution went through several color transitions (i.e. blue to green to colorless). Another absorbance at 264 nm showed an increase in the hydroperoxide decomposition product, N-methylsuccinimide, over time. $Co(NMP)_x$ appears to be the most likely candidate for the resultant highly selective catalyst, functioning in a Class IV[26,27] manner (Figure 3-2).

Another catalyst, $FeCl_3 \cdot 6H_2O$ (Class IVa),[26,27] exhibited behavior similar to that observed in the cobalt-catalyzed experiments, giving a 4:1 epoxide to benzaldehyde ratio.

Good selectivities to epoxide formation in this in situ generated hydroperoxide system employing 1-methyl-2-pyrrolidinone as the solvent were observed with the ruthenium catalyst, $RuCl_3 \cdot 3H_2O$ (Class IVa)[26,27] (Table 3-4). $[Ru_3O(pfb)_6(Et_2O)_3][pfb]$ (Class IVa)[26,27] gave results comparable to the uncatalyzed reaction (Table 3-4).

While the other catalysts employed in the oxidation of trans-β-methylstyrene showed lower selectivities to epoxide than the uncatalyzed reaction, it is surprising to note that the metal oxo epoxidation catalyst, $Mo(O)_2(acac)_2$, showed a predominance of the radical cleavage product, benzaldehyde.

Another metal oxo catalyst, $V(O)(acac)_2$, exhibited a slightly greater preference to the radical cleavage product due to its radical pathway (Class IVa).[26,27]

Another metal oxo precursor, $[Ru(dmp)_2(H_2O)_2][PF_6]_2$, exhibited several interesting observations in the in situ generated 5-hydroperoxo-1-methyl-2-pyrrolidinone system. The Class IVa[26,27] component of this catalyst led to an elimination of the induction period observed in the formation of the hydroperoxide in the uncatalyzed reaction through a metal-catalyzed radical-chain mechanism. The observed color change from purple-red to yellow signals the oxidation of the Ru(II) complex to the Ru(IV)(O) and the $Ru(VI)(O)_2$ species.[118] Two hours into the reaction, this color change was detected. The resulting $Ru(VI)(O)_2$ catalyst reacts with the substrate and is reduced to the Ru(IV)O complex. The Ru(IV)(O) species is then converted back to the $Ru(VI)(O)_2$ species by either hydroperoxide or molecular oxygen to perform further substrate oxidation (Class II or Class III).[26,27]

Using the in situ generated 5-hydroperoxo-1-methyl-2-pyrrolidinone system in the oxidation of trans-β-methyl-styrene, a 1:6 epoxide to benzaldehyde ratio was observed with the $Ru(VI)(O)_2$ species being regenerated by either 5-hydroperoxo-1-methyl-2-pyrrolidinone or molecular oxygen.

Looking at the results given in Table 3-4, the Class IVa[26,27] catalysts (i.e., Co(II), Fe(III), and Ru(III) complexes) with their radical-chain pathways show a surprising selectivity to the formation of 1-phenylpropylene oxide in the

oxidation of trans-β-methylstyrene using the in situ generated hydroperoxide system in 1-methyl-2-pyrrolidinone. When metal oxo catalysts, such as $Mo(O)_2(acac)_2$ and $V(O)(acac)_2$, and the metal oxo precursor, $[Ru(dmp)_2(H_2O)_2][PF_6]_2$, were employed in the oxidation of this olefinic substrate, a preference to the radical cleavage product, benzaldehyde, was observed. As a result of these observations, the nature of these metal-catalyzed oxidations (i.e. homolytic vs. heterolytic oxygen atom transfer) was investigated.

One of the major complications in obtaining mechanistic information on this type of oxidative system is the fact that the in situ formation of the hydroperoxide from 1-methyl-2-pyrrolidinone and molecular oxygen under thermal conditions proceeds by a peroxy-radical mechanism. Earlier studies of the autoxidation of a number of N-alkylamides with the free-radical initiators, t-butyl hydroperoxide, benzoyl hydroperoxide, and α,α-azobis(isobutyronitrile)(AIBN) under thermal conditions support the peroxy-radical mechanism.[5,6,7] With this fact in mind, free-radical inhibitors, such as di-t-butyl-p-cresol (DTBPC), or benzoquinone, would inhibit the in situ hydroperoxide formation; thereby, resulting in no oxidation of the substrate. Likewise, the use of a free-radical initiator would led to an acceleration of the peroxy-radical reaction to form the N-alkylamide hydroperoxide and the subsequent substrate oxidation. These facts led us to further investigate the role played by the transition metal

catalysts in this in situ generated 5-hydroperoxo-1-methyl-2-pyrrolidinone system using a different olefinic substrate.

cis-β-Methylstyrene Oxidation

The aromatic olefinic substrate, cis-β-methylstyrene, was employed in the in situ generated hydroperoxide system in 1-methyl-2-pyrrolidinone solvent to determine the stereoselectivity of the epoxide formation and to aid in the elucidation of the mechanistic pathway by which these metal-catalyzed oxidations proceed.

It is interesting to note that the results given in Table 3-5 for the oxidation of cis-β-methylstyrene show a trend similar to the analogous metal-catalyzed oxidations listed in Table 3-4 for trans-β-methylstyrene. In the oxidation of the cis-olefin, the catalyst, $CoCl_2 \cdot 6H_2O$ (Class IVa),[26,27] was found to be selective to epoxide formation, giving an epoxide to benzaldehyde ratio of 4:1. Another Class a[26,27] catalyst, $RuCl_3 \cdot 3H_2O$, exhibited a 3:1 preference for epoxide formation, while the uncatalyzed reaction gave a 2:1 epoxide to benzaldehyde ratio. On the other hand, a high preference to benzaldehyde formation is observed with the metal oxo catalyst, $Mo(O)_2(acac)_2$ (Class IVb),[26,27] and the metal oxo precursor complex, $[Ru(dmp)_2(H_2O)_2][PF_6]_2$ (Class III),[26,27] giving epoxide to benzaldehyde ratio of 1:6. These observed quantities of the radical cleavage product, benzaldehyde,

Table 3-5 cis-β-Methylstyrene Oxidation.

Catalyst	Epoxide:Benzaldehyde Ratio
none	2.0:1.0 (120 hours)
$CoCl_2 \cdot 6H_2O$	4.0:1.0 (24 hours)
$RuCl_3 \cdot 3H_2O$	3.0:1.0 (24 hours)
$[Ru(dmp)_2(H_2O)_2][PF_6]_2$	1.0:6.0 (24 hours)
$Mo(O)_2(acac)_2$	1.0:6.0 (72 hours)

Note: Reaction conditions:
catalyst (2.3×10^{-5} moles)
substrate (2.3×10^{-2} moles)
NMP (47 mL)
run under O_2 (50 psig) at 75°C.
Completion times given in parentheses.
In all reactions, only the trans-epoxide was observed.

suggest the possible involvement of a radical pathway in the oxidation of olefinic substrates with this in situ generated hydroperoxide system.

Another important factor in determining the role of the transition metal catalyst in the in situ generated 5-hydroperoxo-1-methyl-2-pyrrolidinone system involves the stereoselectivity in the formation of epoxides. As seen in Figure 3-10, the epoxidation of a cis-olefin to a cis-epoxide should proceed by a heterolytic oxygen atom transfer mechanism, while a loss of stereoretention would result from a free-radical intermediate.

In all cases, including the uncatalyzed reaction, only the trans-epoxide was detected. This lack of stereoretention appears to suggest the involvement of a radical pathway in the formation of epoxide using the in situ generated hydroperoxide system in 1-methyl-2-pyrrolidinone. Since a cis-olefin yields a trans-epoxide, the oxidation of the olefin by this oxidative system must allow an opportunity for rotation about the olefinic carbon-carbon bond. This rotation would occur with a radical intermediate.

In our work, the metal-catalyzed oxidations of cis-β-methylstyrene involving Class IVa[26,27] catalysts (i.e. $CoCl_2 \cdot 6H_2O$ and $RuCl_3 \cdot 3H_2O$) show a preference to the formation of the trans-epoxide, providing support for a radical type mechanism with these metal catalysts. Previous work by Kochi and co-workers showed that the cobalt-catalyzed epoxidation of olefins proceeds by a radical chain mechanism using t-butyl

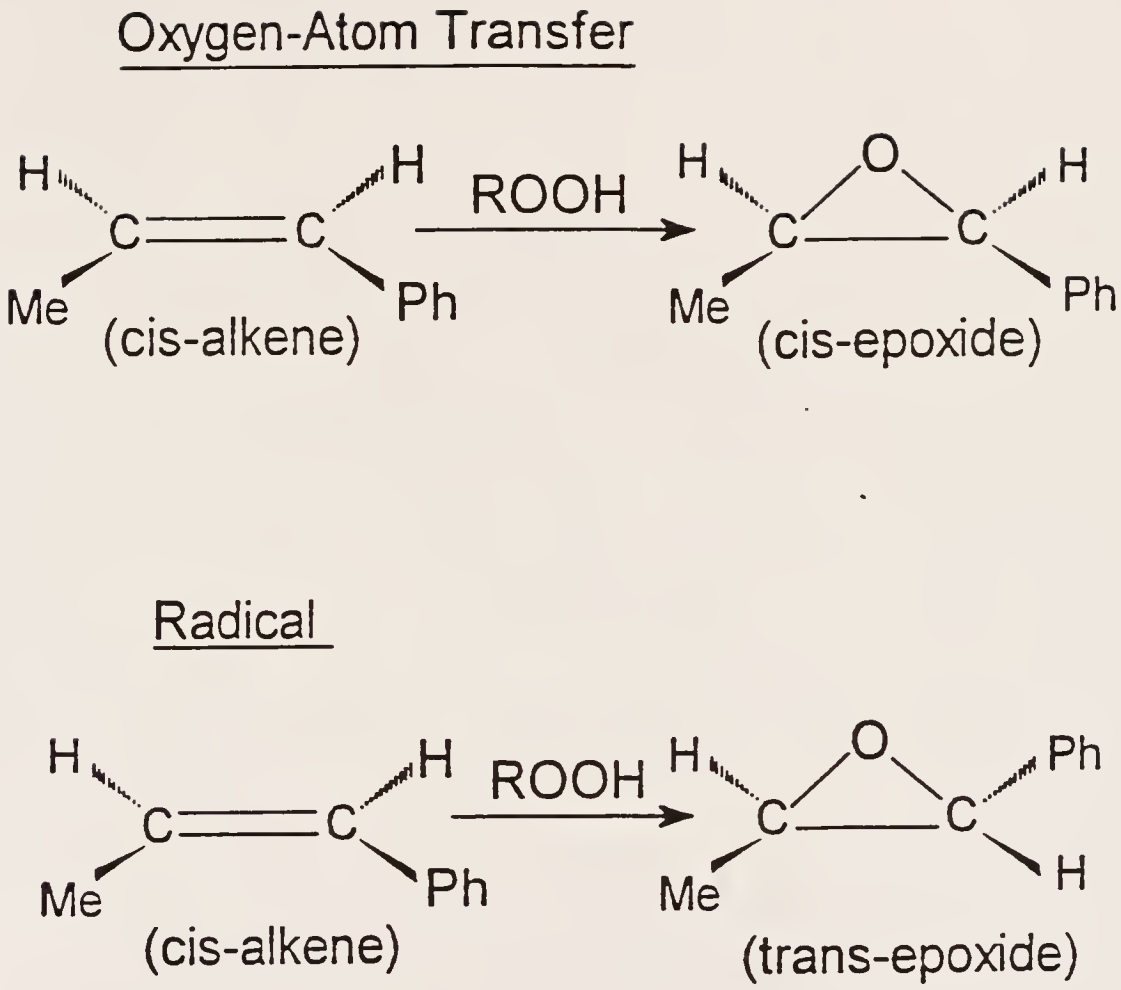


Figure 3-10 Epoxidation Pathways.

hydroperoxide.[57] In this mechanism, the cobalt catalyst interconverts between cobalt(II) and cobalt(III) in the one-electron redox processes leading to the formation of t-butylperoxy-radicals. The subsequent formation of epoxide results from the homolytic addition of the t-butylperoxy-radical to the carbon-carbon double bond.

When the metal oxo precursor complex, $[Ru(dmp)_2(H_2O)_2][PF_6]_2$, was employed in the oxidation of cis-β-methylstyrene in the in situ generated 5-hydroperoxo-1-methyl-2-pyrrolidinone system, a large amount of benzaldehyde results. In addition to the radical cleavage product, the epoxidation of the cis-olefin gave only the trans-epoxide. The lack of stereoretention in epoxide formation as well as the prevalence of carbon-carbon double bond cleavage during the oxidation of olefins by $Ru(VI)O_2$ complexes can be accounted for by a homolytic process involving oxygen atom transfer (Class III character with Class IVa component).[26,27] This type of reactivity has been reported by Kochi and co-workers for a general class of neutral, non-halogen-containing complexes of the type $O_2RuL_2Y_2$ (where L=pyridine and Y=a carboxylato ligand).[119]

$Mo(O)_2(acac)_2$ (Class IVb)[26,27] has been investigated as a catalyst for the epoxidation of cis-β-methylstyrene with t-butyl hydroperoxide at 70°C by Endo et al.[75] In their study, the stereoretention was maintained as a result of an oxygen atom transfer mechanism. When this catalyst was employed in the oxidation of cis-β-methylstyrene in the in situ generated

5-hydroperoxo-1-methyl-2-pyrrolidinone system, a high selectivity to benzaldehyde resulted. This metal-catalyzed reaction showed a loss of stereoretention in the formation of epoxide by yielding only the trans-epoxide. This result would seem to suggest the involvement of an oxygen atom transfer possessing radical character, yet earlier literature reportings describe the epoxidations of various olefins occuring by heterolytic oxygen atom transfer mechanisms (Class IVb).[26,27] As a result of this discrepency, the effects of solvents on the $Mo(O)_2(acac)_2$ catalyzed oxidation of these olefinic substrates were pursued.

Solvent Effects

Another interesting aspect in the oxidation of trans-β-methylstyrene using $Mo(O)_2(acac)_2$ as the catalyst involves the observation of a solvent dependency on the epoxide to benzaldehyde ratio. In a number of previous studies, molybdenum complexes have been shown to be highly selective to epoxide formation when run in non-polar solvents, such as benzene or CCl_4.[74,75] The predominance of benzaldehyde observed in the in situ generated 5-hydroperoxo-1-methyl-2-pyrrolidinone system catalyzed by $Mo(O)_2(acac)_2$ led us to perform an oxidant/solvent variation study. Looking at Table 3-6, the use of the polar solvent, 1-methyl-2-pyrrolidinone, with either 5-hydroperoxo-1-methyl-2-pyrrolidinone (in situ or pre-generated) or t-butyl hydroperoxide in the presence of the molybdenum catalyst showed a preference to benzaldehyde. An

Table 3-6 Solvent Effects in the Oxidation of trans-β-Methylstyrene with $Mo(O)_2(acac)_2$ Catalyst.

Solvent	Oxidant	E/B
NMP	NMP-5-OOH (in situ)	1:3.4
NMP	NMP-5-OOH (pre-generated)	1:2
NMP	t-BuOOH	1:2
DMA	t-BuOOH	1:3
Benzene	t-BuOOH	4:1
1,4-dioxane	t-BuOOH	7:1
CCl_4	t-BuOOH	10:1

Note: Reaction conditions:
substrate (2.3×10^{-2} moles)
catalyst (2.3×10^{-5} moles)
solvent (47 mL)
oxidant (2.3×10^{-2} moles, if added)
run at 75°C under N_2, except NMP-5-OOH (in situ) O_2 (50 psig).
E/B values at 48 hours, except NMP-5-OOH (in situ).

analogous preference to benzaldehyde formation was observed in the polar solvent, dimethylacetamide, using t-butyl hydroperoxide. Using $Mo(O)_2(acac)_2$ and t-butyl hydroperoxide, non-polar solvents, such as benzene, 1,4-dioxane, or CCl_4, gave a high selectivity to the formation of trans-1-phenylpropylene oxide. This comparison study definitely shows a dependency of the epoxide to benzaldehyde ratio on the polarity of the solvent.

Even though a much less pronounced solvent effect on the epoxide to benzaldehyde ratio was observed in the $Mo(O)_2(acac)_2$-catalyzed oxidation of cis-β-methylstyrene, the observed stereoretention (or lack of) in the formation of epoxide shows a solvent dependency with the oxidant t-butyl hydroperoxide (Table 3-7). In the polar solvents, dimethylacetamide and 1-methyl-2-pyrrolidinone, the oxidation of cis-β-methylstyrene resulted in the formation of trans-1-phenylpropylene oxide. This observed lack of stereoretention in the formation of the corresponding epoxide and the predominance of benzaldehyde formation seem to suggest the involvement of a radical type mechanism (Class IVa),[26,27] yet it is interesting to note that the employment of non-polar solvents, such as benzene, CCl_4, or 1,4-dioxane, leads to the formation of cis-1-phenylpropylene oxide from the corresponding cis-olefin (Table 3-7). The retention of configuration seen in these non-polar solvents appear to suggest the involvement of a heterolytic oxygen atom transfer mechanism (Class IVb).[26,27] As a result of these observations,

Table 3-7 Solvent Effects in the Oxidation of cis-β-Methylstyrene With $Mo(O)_2(acac)_2$ Catalyst.

Solvent	Oxidant	E/B	Epoxide (cis/trans)
NMP	NMP-5-OOH (in situ)	1:6	(0/14%)
NMP	NMP-5-OOH (pre-gen)	1:6	(0/6%)
NMP	t-BuOOH	1:7	(0/5%)
DMA	t-BuOOH	1:8	(0/5%)
Benzene	t-BuOOH	1:5	(5%/0)
1,4-dioxane	t-BuOOH	1:4	(8%/0)
CCl_4	t-BuOOH	1:2	(12%/0)

Note: Reaction conditions:
substrate (2.3×10^{-2} moles)
catalyst (2.3×10^{-5} moles)
solvent (47 mL)
oxidant (2.3×10^{-2} moles, if added)
run at 75°C under N_2, except NMP-5-OOH (in situ) O_2 (50 psig).
Reactions run in 48 hours, except NMP-5-OOH (in situ).

the exact nature of the mechanistic pathway by which these $Mo(O)_2(acac)_2$-catalyzed oxidations occurs was further investigated using the halocarbons, CCl_4 and CBr_4 to determine if these reactions occur via a homolytic (Class IVa)[26,27] or a heterolytic (Class IVb)[26,27] process.

Halocarbon Additions

A series of experiments were designed to determine the mechanistic pathway by which the molybdenum-catalyzed oxidation of trans-β-methylstyrene occurs in the polar solvent, 1-methyl-2-pyrrolidinone. Looking at Table 3-8, the addition of a halocarbon (CCl_4 or CBr_4) to the $Mo(O)_2(acac)_2$-catalyzed olefin oxidation using either pre-generated 5-hydroperoxo-1-methyl-2-pyrrolidinone or t-butyl hydroperoxide as the oxidant showed only the formation of benzaldehyde and trans-1-phenylpropylene oxide. No halogenated products were detected; thereby, ruling out a radical process. This absence of halogenated products suggests the involvement of a heterolytic oxygen atom transfer mechanism involving a lack of stereoretention in polar solvents, such as 1-methyl-2-pyrrolidinone. The above results shows or Class IVb behavior for the metal catalyst, $Mo(O)_2(acac)_2$.[26,27]

Effects of Added Pyridine

The addition of a catalytic amount of pyridine to the $Mo(O)_2(acac)_2$-catalyzed oxidation of trans-β-methylstyrene was

Table 3-8 trans-β-Methylstyrene Oxidation in the Presence of Halocarbons.

Halocarbon	Oxidant	Products (%)
CCl_4	NMP-5-OOH (pre-gen)	Benzaldehyde (24) Epoxide (12)
CCl_4	t-BuOOH	Benzaldehyde (24) Epoxide (10)
CBr_4	NMP-5-OOH (pre-gen)	Benzaldehyde (24) Epoxide (12)
CBr_4	t-BuOOH	Benzaldehyde (28) Epoxide (12)

Note: Reaction conditions:
substrate (2.3×10^{-2} moles)
catalyst (2.3×10^{-5} moles)
halocarbon (2.3×10^{-2} moles)
oxidant (2.3×10^{-2} moles)
run under N_2 at 75°C for 48 hours.
No other products, including halogenated hydrocarbons, were detected by GC or ^{13}C and ^{1}H NMR.

investigated using 5-hydroperoxo-1-methyl-2-pyrrolidinone (in situ or pre-generated) and t-butyl hydroperoxide in the solvents 1-methyl-2-pyrrolidinone and CCl_4 under the reaction conditions given in Table 3-9. The comparison of reactions with and without the added aromatic amine presented in Table 3-9 show a marked effect on the epoxide to benzaldehyde ratio when a catalytic amount of pyridine is added to the reaction. In the cases employing added pyridine, trans-1-phenylpropylene oxide is the predominant product.

It is interesting to note that the use of pyridine as the solvent in the oxidation of cis- or trans-β-methylstyrene using $Mo(O)_2(acac)_2$ and t-butyl hydroperoxide gave epoxide to benzaldehyde ratios of 1:3 and 7:1, respectively. These results suggests a dependence on the polarity of the solvent.

The effects of solvent polarity on the molybdenum-catalyzed oxidation of cis-β-methylstyrene show a noticeable effect on the epoxide to benzaldehyde ratio with the addition of a catalytic amount of pyridine (Table 3-10). The use of the polar solvents like 1-methyl-2-pyrrolidinone lead to a lack of stereoretention, while the use of non-polar solvents like CCl_4 show a retention of configuration. Similar results have been previously reported by Endo et al. for the reaction of cis-β-methylstyrene with t-butyl hydroperoxide and $Mo(O)_2(acac)_2$ in CCl_4 at elevated temperatures.[75]

Attempts were made to determine the role played by the added pyridine in these metal-catalyzed oxidations. The substitution of pyridine N-oxide for pyridine was investigated

Table 3-9 Effect of Added Pyridine on the $Mo(O)_2(acac)_2$-Catalyzed Oxidation of trans-β-Methylstyrene.

Solvent	Oxidant	Pyridine	E/B
NMP	NMP-5-OOH (in situ)	No	1.0:3.4
NMP	NMP-5-OOH (in situ)	Yes	1.6:1.0
NMP	NMP-5-OOH (pre-gen)	No	1.0:2.0
NMP	NMP-5-OOH (pre-gen)	Yes	1.2:1.0
NMP	t-BuOOH	No	1.0:2.0
NMP	t-BuOOH	Yes	2.0:1.0
CCl_4	t-BuOOH	No	10.0:1.0
CCl_4	t-BuOOH	Yes	24.0:1.0

Note: Reaction conditions:
substrate (2.3×10^{-2} moles)
catalyst (2.3×10^{-5} moles)
pyridine (2.3×10^{-5} moles, if added)
solvent (47 mL)
oxidant (2.3×10^{-2} moles, if added)
run under N_2 at 75°C, except NMP-5-OOH (in situ)
O_2 (50 psig).
Reactions run 48 hours, except NMP-5-OOH (in situ).

Table 3-10 Effect of Added Pyridine on the $Mo(O)_2(acac)_2$-Catalyzed Oxidations of cis-β-Methylstyrene.

Solvent	Oxidant	E/B	Epoxide (cis/trans)
NMP	NMP-5-OOH (in situ)	1:2	(0/38%)
NMP	NMP-5-OOH (pre-gen)	1:3	(0/21%)
NMP	t-BuOOH	1:3	(0/20%)
CCl_4	t-BuOOH	3:1	(40%/0)

Note: Reaction conditions:
substrate ($2.3x10^{-2}$ moles)
catalyst ($2.3x10^{-5}$ moles)
pyridine ($2.3x10^{-5}$ moles)
solvent (47 mL)
oxidant ($2.3x10^{-2}$ moles, if added)
run under N_2 at 75°C, except NMP-5-OOH (in situ) O_2 (50 psig).
Reactions were run for 48 hours, except NMP-5-OOH (in situ).

in the solvents, 1-methyl-2-pyrrolidinone and CCl_4, using either 5-hydroperoxo-1-methyl-2-pyrrolidinone (in situ or pre-generated) or t-butyl hydroperoxide. The observed epoxide to benzaldehyde ratios for these molybdenum-catalyzed reactions were similar to the analogous reactions containing the added pyridine (Tables 3-11 and 3-12). Reactions involving the use of cis-β-methylstyrene as the substrate showed formation of the trans-epoxide in the polar solvent, 1-methyl-2-pyrrolidinone, and formation of the cis-epoxide in the non-polar solvent, CCl_4 (Table 3-12).

An evaluation of the possible formation of pyridine-N-oxide from the corresponding aromatic amine and molecular oxygen was performed at 75°C in the presence of the metal catalyst, $Mo(O)_2(acac)_2$, using trans-β-methylstyrene as the olefinic substrate. After 48 hours of reaction in CCl_4, no oxidation products were detected. As discussed earlier, the analogous reaction containing t-butyl hydroperoxide showed oxidation of the substrate with a predominance in the formation of the trans-epoxide. These experiments demonstrate the necessity of the alkyl hydroperoxides in this catalytic system.

The Mo(VI)-catalyzed oxidations of a number of heterocyclic amines have been reported in the literature using a variety of alkyl hydroperoxides as the oxidants.[120-123] In one early report, Shang and Zajacek described the oxidation of pyridine to the cooresponding amine oxide using t-butyl hydroperoxide in the presence of a molybdenum catalyst at

Table 3-11 Effect of Added Pyridine-N-oxide on $Mo(O)_2(acac)_2$-Catalyzed Oxidation of trans-β-Methylstyrene.

Solvent	Oxidant	Py or PyO	E/B
NMP	NMP-5-OOH (in situ)	Py	1.6:1
NMP	NMP-5-OOH (in situ)	PyO	2:1
NMP	NMP-5-OOH (pre-gen)	Py	2:1
NMP	NMP-5-OOH (pre-gen)	PyO	2:1
NMP	t-BuOOH	Py	2.2:1
NMP	t-BuOOH	PyO	2:1
CCl_4	t-BuOOH	Py	24:1
CCl_4	t-BuOOH	PyO	18:1

Note: Reaction conditions:
substrate (2.3×10^{-2} moles)
catalyst (2.3×10^{-5} moles)
py (or PyO) (2.3×10^{-5} moles, if added)
solvent (47 mL)
oxidant (2.3×10^{-2} moles, if added)
run under N_2 at 75°C, except NMP-5-OOH (in situ) O_2 (50 psig).
All reactions run 48 hours, except NMP-5-OOH (in situ).

Table 3-12 Effect of Added Pyridine-N-oxide on the $Mo(O)_2(acac)_2$-Catalyzed Oxidation of cis-β-Methylstyrene.

Solvent	Oxidant	E/B	Epoxide (cis/trans)
NMP	NMP-5-OOH (in situ)	1:2	(0/40)
NMP	NMP-5-OOH (pre-gen)	1:3	(0/20)
NMP	t-BuOOH	1:2	(0/30)
CCl_4	t-BuOOH	4:1	(50%/0)

Note: Reaction conditions:
substrate ($2.3x10^{-2}$ moles)
catalyst ($2.3x10^{-5}$ moles)
pyridine-N-oxide ($2.3x10^{-5}$ moles)
solvent (47 mL)
oxidant ($2.3x10^{-2}$ moles, if added)
run under N_2 at 75°C, except NMP-5-OOH (in situ)
O_2 (50 psig).
Reactions were run for 48 hours, except NMP-5-OOH (in situ).

elevated temperatures.[120] After 120 hours under our reaction conditions, the oxidation of pyridine was found to give low yields of the amine oxide (Table 3-13). The low yields obtained can be explained by the ability of amines and amine oxides to form complexes with metals.[120] This allows them to compete with the alkyl hydroperoxide in complexing with the catalyst. This effect has been shown with pyridine. In the initial stages of the reaction, the conversion of the hydroperoxide was very rapid; therefore, the pyridine did not seem to be complexing with the catalyst. As the concentration of amine oxide increased, the rate of reaction was retarded. Formation of a white precipitate, containing both molybdenum and pyridine-N-oxide, was obtained.[120] Furthermore, high conversions and yields of the aromatic amine oxide were obtained using larger alkyl hydroperoxide to pyridine ratios. The higher alkyl hydroperoxide concentration allows it to compete with the amine oxide for the catalyst.

In another series of experiments, the utilization of pyridine-N-oxide as an oxidant in the metal-catalyzed oxidation of trans-β-methylstyrene was investigated. The results given in Table 3-14 show a high selectivity to the formation of trans-1-phenylpropylene oxide. Even after 120 hours of reaction, these metal-catalyzed oxidations showed very low yields of epoxide in both non-polar and polar solvents. This is not surprising, since heterocyclic aromatic amine-N-oxides are less reactive oxidants than aliphatic amine-N-oxides. Based on the experimental information pre-

Table 3-13 Pyridine Oxidations.

Solvent	Oxidant	Products (%)
NMP	NMP-5-OOH (in situ)	PyO (trace)
NMP	NMP-5-OOH (pre-gen)	PyO (2)
NMP	t-BuOOH	PyO (5)
CCl_4	t-BuOOH	PyO (13)

Note: Reaction conditions:
pyridine (1.0×10^{-1} moles)
catalyst (2.0×10^{-4} moles, $Mo(O)_2(acac)_2$)
solvent (30 mL, except NMP-5-OOH (in situ) 42mL)
oxidant (1.0×10^{-1} moles, if added)
run under N_2 at 75°C, except NMP-5-OOH (in situ)
O_2 (50 psig).
Reactions run 120 hours.

Table 3-14 trans-β-Methylstyrene Oxidation Using Pyridine-N-oxide.

Solvent	Catalyst	Products (%)
NMP	No	none
NMP	Yes	trans-epoxide (1)
CCl_4	No	none
CCl_4	Yes	trans-epoxide (1)

Note: Reaction conditions:
substrate (2.3×10^{-2} moles)
catalyst (2.3×10^{-5} moles, $Mo(O)_2(acac)_2$, if added)
pyridine-N-oxide (2.3×10^{-2} moles)
solvent (47 mL)
run under N_2 at 75°C.
Reactions were run 120 hours.

sented, the possible involvement of an in situ generated pyridine-N-oxide as an active oxidant in this catalytic system appears to be unlikely.

Substitution of the substituted pyridines, 2-picoline and 2,6-lutidine, for pyridine in the $Mo(O)_2(acac)_2$-catalyzed oxidations of cis- and trans-β-methylstyrene in non-polar and polar solvents showed a dependence of the steric hinderance of the aromatic amine on the epoxide to bezaldehyde ratio (Tables 3-15 and 3-16). Compared to the experimental runs containing no added amine, the sterically-hindered 2,6-lutidine showed no effect on the epoxide to benzaldehyde ratio for the cis- and trans-olefins. The use of the less sterically-hindered 2-picoline exhibited no effect on the epoxide to benzaldehyde ratios in the cis-β-methylstyrene oxidations, but showed an increase in the formation of epoxide in the trans-β-methylstyrene cases. These results suggest that the increase in the steric bulk around the nitrogen donor of the aromatic amine has diminishing effect on the increase in epoxide formation, which may be due to decreased ability of the aromatic amine to interact with the metal species.

In order to evaluate the possibility of the coordination of the pyridine with the metal, a ^1H NMR study of the reaction of $Mo(O)_2(acac)_2$ and pyridine was performed in CCl_4 and 1-methyl-2-pyrrolidinone. When compared with the ^1H NMR spectra for free pyridine in each of these solvents, the reactions containing $Mo(O)_2(acac)_2$ and pyridine exhibited no changes in the chemical shifts for the pyridine resonances. Analogous

Table 3-15 Use of Substituted Pyridines in the Oxidation of cis-β-Methylstyrene.

Solvent	Aromatic Amine	E/B
CCl_4	none	1:2
CCl_4	pyridine	3:1
CCl_4	2-picoline	1:2.8
CCl_4	2,6-lutidine	1:2.6
NMP	none	1:7
NMP	pyridine	1:3
NMP	2-picoline	1:7
NMP	2,6-lutidine	1:6

Note: Reaction conditions:
substrate (2.3×10^{-2} moles)
catalyst (2.3×10^{-5} moles, $Mo(O)_2(acac)_2$)
aromatic amine (2.3×10^{-5} moles)
solvent (47 mL)
t-BuOOH (2.3×10^{-2} moles)
run under N_2 at 75°C for 48 hours.

Table 3-16 Use of Substituted Pyridines in the Oxidation of trans-β-Methylstyrene.

Solvent	Aromatic Amine	E/B
CCl_4	none	10:1
CCl_4	pyridine	24:1
CCl_4	2-picoline	14:1
CCl_4	2,6-lutidine	9:1
NMP	none	1:2
NMP	pyridine	2.2:1
NMP	2-picoline	1.4:1
NMP	2,6-lutidine	1:2.2

Note: Reaction conditions:
substrate (2.3×10^{-2} moles)
catalyst (2.3×10^{-5} moles, $Mo(O)_2(acac)_2$)
aromatic amine (2.3×10^{-5} moles)
solvent (47 mL)
t-BuOOH (2.3×10^{-2} moles)
run under N_2 at 75°C for 48 hours.

results were obtained for the reaction of $Mo(O)_2(acac)_2$ and pyridine in the presence of t-butyl hydroperoxide. These results suggest that the pyridine is not coordinated to the metal when pyridine is reacted with $Mo(O)_2(acac)_2$ in a 1:1 molar ratio. Several possible roles for the enhancement of epoxide formation will be discussed in the next section.

Active Species for $Mo(O)_2(acac)_2$ Reactions

It has generally been accepted that the active species in the epoxidation of alkenes by alkyl hydroperoxides contains an alkylperoxo ligand coordinated to the metal in either a linear or triangular fashion (Figure 3-6)[79] in a distorted octahedral complex. Since most of the catalyst precursors are octahedral themselves, it is necessary for a ligand to dissociate to create a vacant site(s) for coordination of the alkylperoxo ligand. One such possibility involves the reduction of the cis-dioxomolybdenum(VI) complexes by oxo transfer to an organic substrate, producing a coordinatively unsaturated mono oxomolybdenum(IV) species,[124,125] which could react with alkyl hydroperoxides to form the mono oxomolybdenum(VI) alkylperoxo active species. To test this possible route, $Mo(O)_2(acac)_2$ and trans-β-methylstyrene (1:1 molar ratio) were reacted at 75°C under an inert atmosphere in CCl_4 and 1-methyl-2-pyrrolidinone. No oxidation products were detected in either reaction; therefore, eliminating the possible reaction of the high-valent metal oxo complex with the olefinic substrate (Class III).[26,27]

The other possibility involves the reaction of the bidentate acetylacetonate ligand with t-butyl hydroperoxide to form a coordinated alkylperoxo ligand. When reacted with t-butyl hydroperoxide, the acetylacetonate ligands were found by ^1H NMR to produce acetylacetone and dissociate from the metal center. Analogous dissociative behavior was detected using 1-methyl-2-pyrrolidinone as well.

In addition to the observed acetylacetonate dissociation, the ^1H NMR spectrum of the reaction of $Mo(O)_2(acac)_2$ and t-butyl hydroperoxide in CCl_4 contained two additional resonances at +2.02 and +2.10 ppm (Table 3-17). The ^1H NMR study of the oxidation of styrene by the complex, V(O)(OOR)(R-OPhsal-R) (where R=^{t}Bu and R-OPhsal-R=N-(2-oxidophenyl)-salicylidenaminato), showed the appearance of a resonance downfield of the coordinated alkylperoxy resonance.[73] This resonance was attributed to the coordinated alkoxy group. Assuming this trend holds for molybdenyl complexes, the resonances detected at +2.02 and +2.10 ppm are attributed to the t-butyl functionalities on the coordinated alkylperoxy and alkoxy groups, respectively. The addition of t-butyl alcohol to the reaction showed an increase in the intensity of the +2.10 ppm resonance. The observed downfield shift for the coordinated alkylperoxo group with respect to free t-butyl hydroperoxide ($\Delta\delta$=0.92ppm) is characteristic of a triangular metal alkylperoxo arrangement,[50,73] which is though to be the

Table 3-17 ^{1}H NMR Results for $Mo(O)_2(acac)_2$/t-Butyl Hydroperoxide Reactions.

Solvent	δ(ppm)	Species
CCl_4	1.10	t-BuOOH
	1.20	t-BuOOH
	1.80	acac
	1.92	$Mo(O)_2(acac)_2$
	1.96	$Mo(O)_2(acac)_2$
	2.02	Mo-O-O-^{t}Bu (triangular)
	2.10	Mo-O-^{t}Bu
	5.20	acac
	5.50	$Mo(O)_2(acac)_2$
TMS	0.96	t-BuOOH
	1.16	t-BuOOH
	1.45	Mo-O-O-^{t}Bu (linear)
	1.72	acac
	1.74	Mo-O-^{t}Bu
	1.78	$Mo(O)_2(acac)_2$
	1.82	$Mo(O)_2(acac)_2$
	5.34	acac
	5.70	$Mo(O)_2(acac)_2$

active species. The use of non-associating non-polar solvents facilitates the formation of the triangular metal alkylperoxo species.

The reaction of $Mo(O)_2(acac)_2$ and t-butyl hydroperoxide in tetramethylene sulfone was analyzed by ^1H NMR to determine the nature of the active species in polar solvents. The two additional resonances detected at +1.45 and +1.74ppm in this system are attributable to the t-butyl functionalities on the coordinated alkylperoxo and alkoxy groups, respectively (Table 3-17). The addition of t-butyl alcohol to the reaction resulted in an increase in the intensity of the +1.74ppm resonance. Compared to the results for the analogous reaction in CCl_4, a lower downfield shift for the coordinated alkylperoxo group with respect to free t-butyl hydroperoxide ($\Delta\delta$=0.49ppm) was observed. Since lower downfield shifts have been observed for a linear metal alkylperoxo arrangement,[126] the resonance of +1.45ppm would suggest this type of active species in polar solvents, such as 1-methyl-2-pyrrolidinone. The linear metal alkylperoxo arrangement can be rationalized by the possible association of a solvent molecule with the metal center; therefore, blocking a vacant coordination site and leading to a linear metal alkylperoxo species. These results suggest the involvement of a mechanism(s) of a Class IVb[26,27] nature.

Possible Mechanistic Pathways for Molybdenum-Catalyzed Epoxidations

In the previous section, spectroscopic evidence supporting the involvement of a metal alkylperoxo species in the $Mo(O)_2(acac)_2$-catalyzed oxidation of alkenes using t-butyl hydroperoxide was presented. These reactions involve a mechanism(s) possessing Class IVb behavior.[26,27]

The results for the oxidation of olefins in non-polar solvents seems to suggest that the active triangular metal alkylperoxo species is more selective to epoxide formation. In non-polar solvents, the stereoselective epoxide formation observed in the $Mo(O)_2(acac)_2$-catalyzed reactions can be explained by a Sharpless-like mechanism (Figure 3-11). This heterolytic mechanism is in agreement with the observed stereoretention seen in the formation of epoxide. Two possible mechanisms for the formation of the small amounts of observed cleavage products in non-polar solvents are given (Figures 3-12 and 3-13). In the presence of a catalytic amount of pyridine, the observed increase in the amount of epoxide could be the result of a facile ligand substitution process, which facilitates the dissociation of the epoxide from the intermediate metal species. This facilitated dissociation of the epoxide from the metal species by pyridine reduces the chance of cleavage product formation.

In the case of polar solvents, the experimental results presented earlier seem to suggest that the resulting linear metal alkylperoxo species is less selective to epoxide

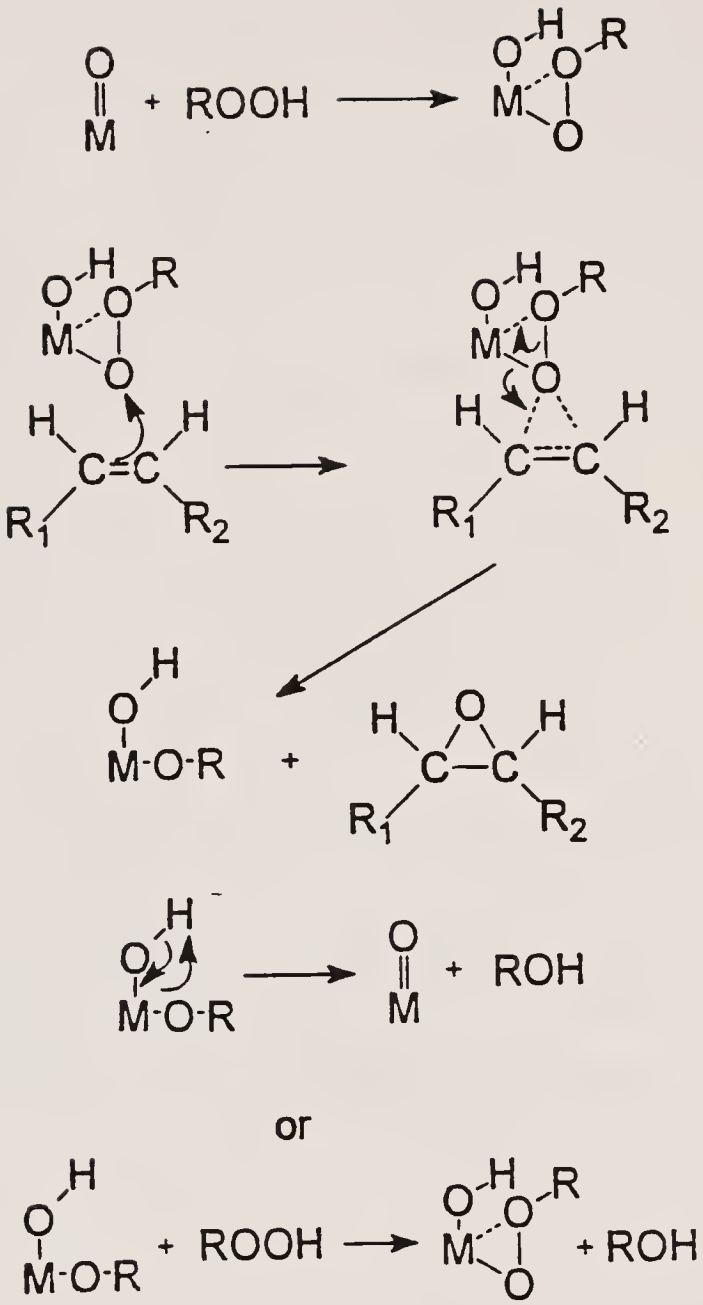


Figure 3-11 Stereoselective Epoxidation in Non-polar Solvents.

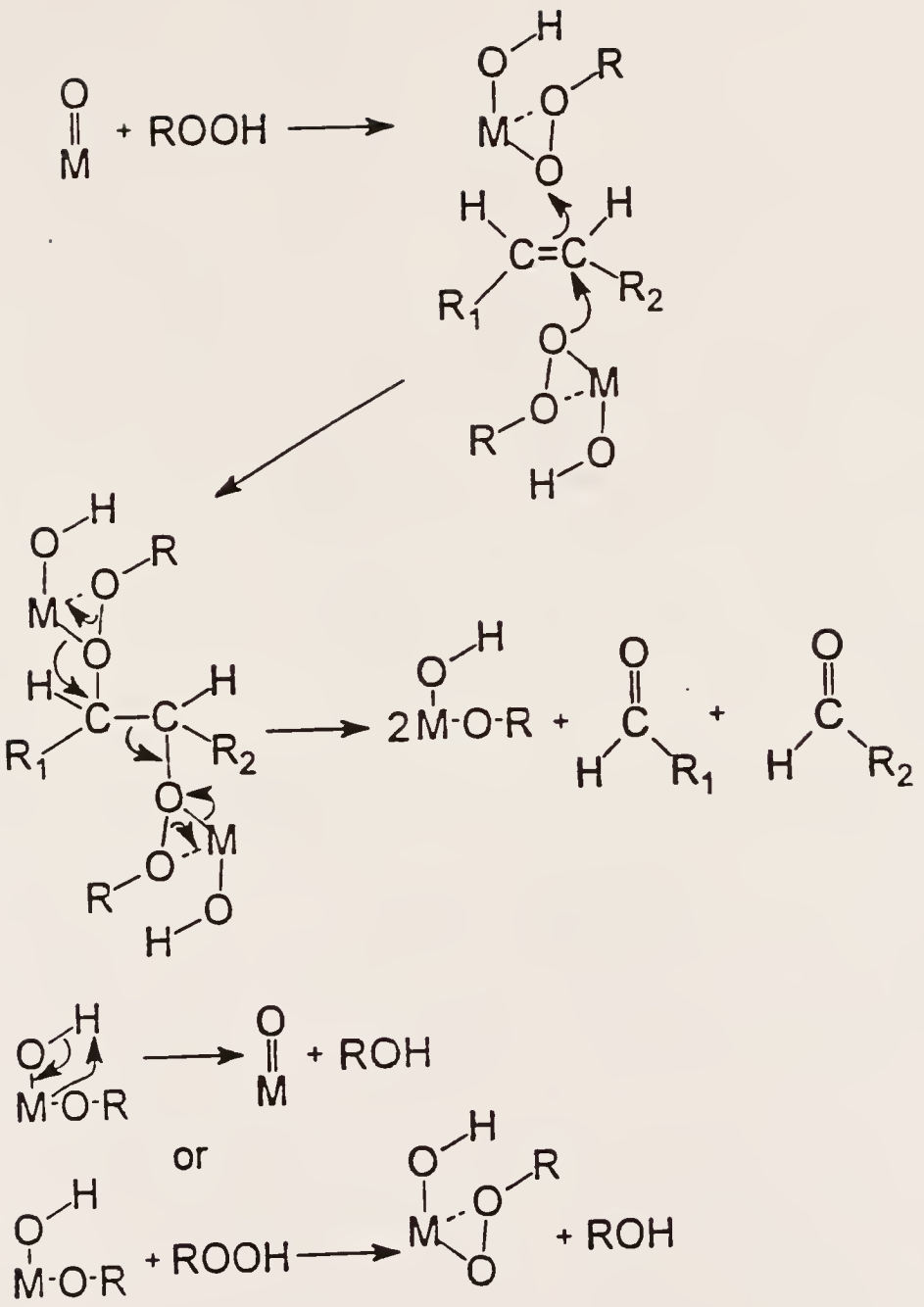


Figure 3-12 Benzaldehyde Formation in Non-polar Solvents.

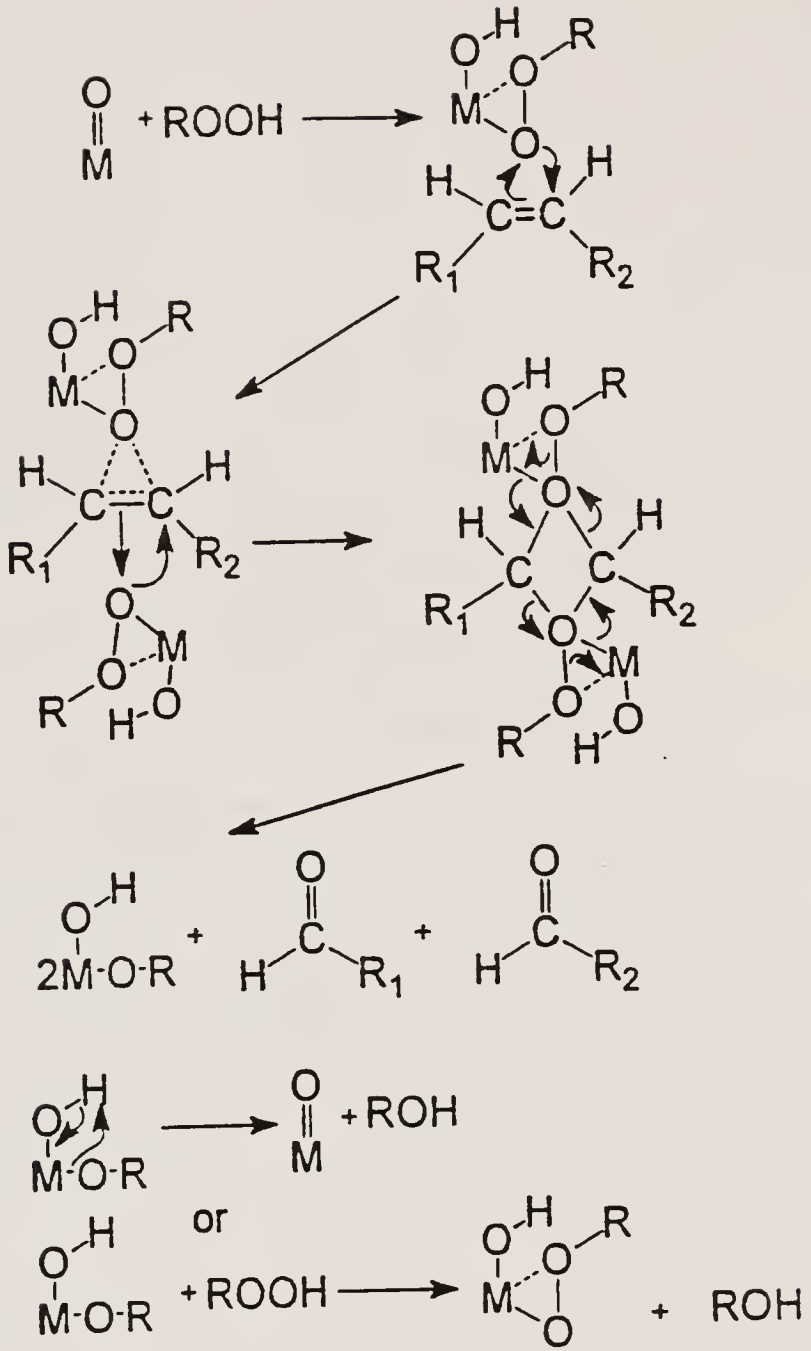


Figure 3-13 Benzaldehyde Formation in Non-polar Solvents.

formation. The lack of stereoretention observed in non-polar solvents, such as 1-methyl-2-pyrrolidinone, most likely involves a metal intermediate species which allows for rotation about the carbon-carbon bond. A possible mechanism for the non-stereoselective epoxide formation involving a carbonium ion intermediate is shown (Figure 3-14).

It is interesting to note that the use of $CHCl_3$, with its potential for possible interaction with the oxygen directly attached to the t-butyl group on the alkylperoxo functionality, does not lead to an increase in the amount of epoxide relative to the CCl_4 results (Table 3-18). This suggests that the solvent polarity performs a major role in the nature of the active metal alkylperoxo species.

A possible mechanism for the observed formation of benzaldehyde is shown in Figure 3-15. This possible reaction scheme involves the reaction of two metal alkylperoxo species to one alkene molecule. At very low concentrations of metal catalyst, this type of reactivity would probably be unlikely.

Another possible mechanism involving a metal-dioxetane-type intermediate is shown in Figure 3-16. This possible pathway seems very unlikely due to the very unfavorable breakage of the carbon-oxygen bond of the alkylperoxo group in the dioxetane intermediate to give an alkyl carbonium ion and the cleavage products.

Benzaldehyde formation in polar solvents could possibly result from a Baeyer-Villiger-type mechanism involving oxygen atom insertion into the carbon-carbon bond of the

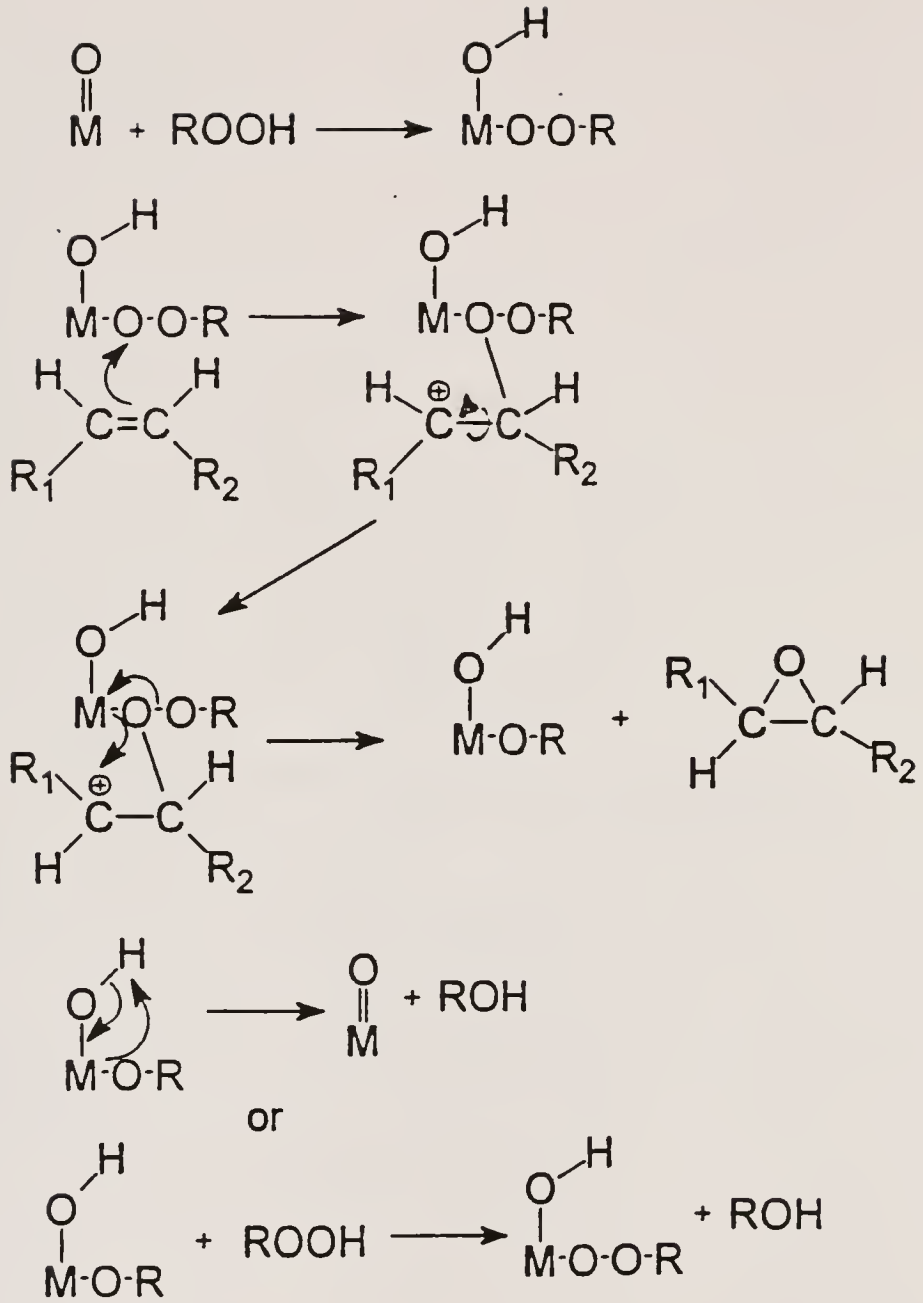


Figure 3-14 Non-stereoselective Epoxidation in Polar Solvents.

Table 3-18 cis- and trans-β-Methylstyrene Oxidation in $CHCl_3$ and CCl_4.

Substrate	Solvent	Pyridine	E/B
cis-β-MS	$CHCl_3$	No	1:3
cis-β-MS	$CHCl_3$	Yes	2:1
cis-β-MS	CCl_4	No	1:2
cis-β-MS	CCl_4	Yes	3:1
trans-β-MS	$CHCl_3$	No	9:1
trans-β-MS	$CHCl_3$	Yes	15:1
trans-β-MS	CCl_4	No	10:1
trans-β-MS	CCl_4	Yes	24:1

Note: Reaction conditions:
substrate (2.3×10^{-2} moles)
catalyst (2.3×10^{-5} moles, $Mo(O)_2(acac)_2$)
solvent (47 mL)
t-BuOOH (2.3×10^{-2} moles)
pyridine (2.3×10^{-5} moles, if added)
run under N_2 at 75°C for 48 hours.

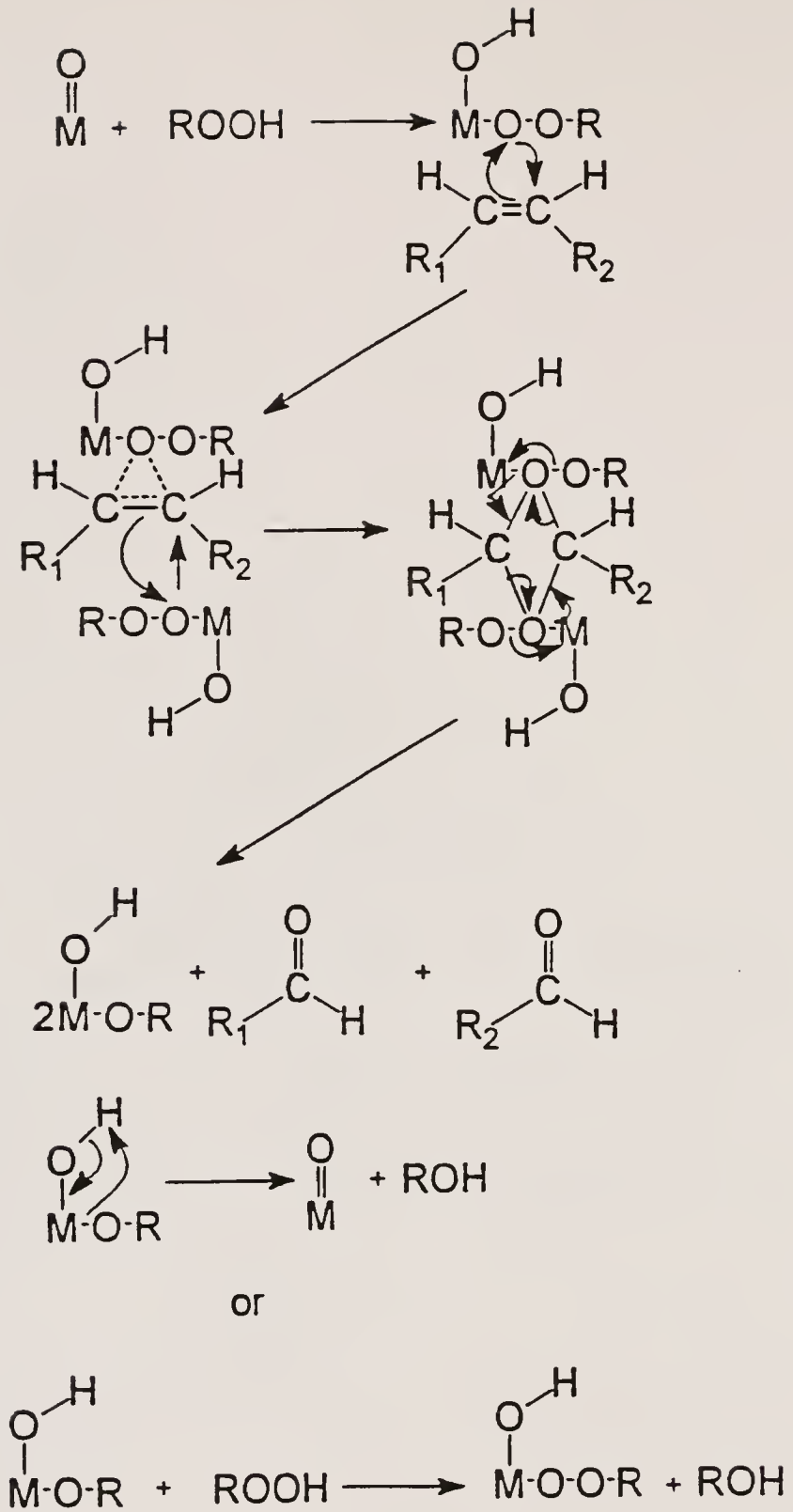


Figure 3-15 Benzaldehyde Formation in Polar Solvents.

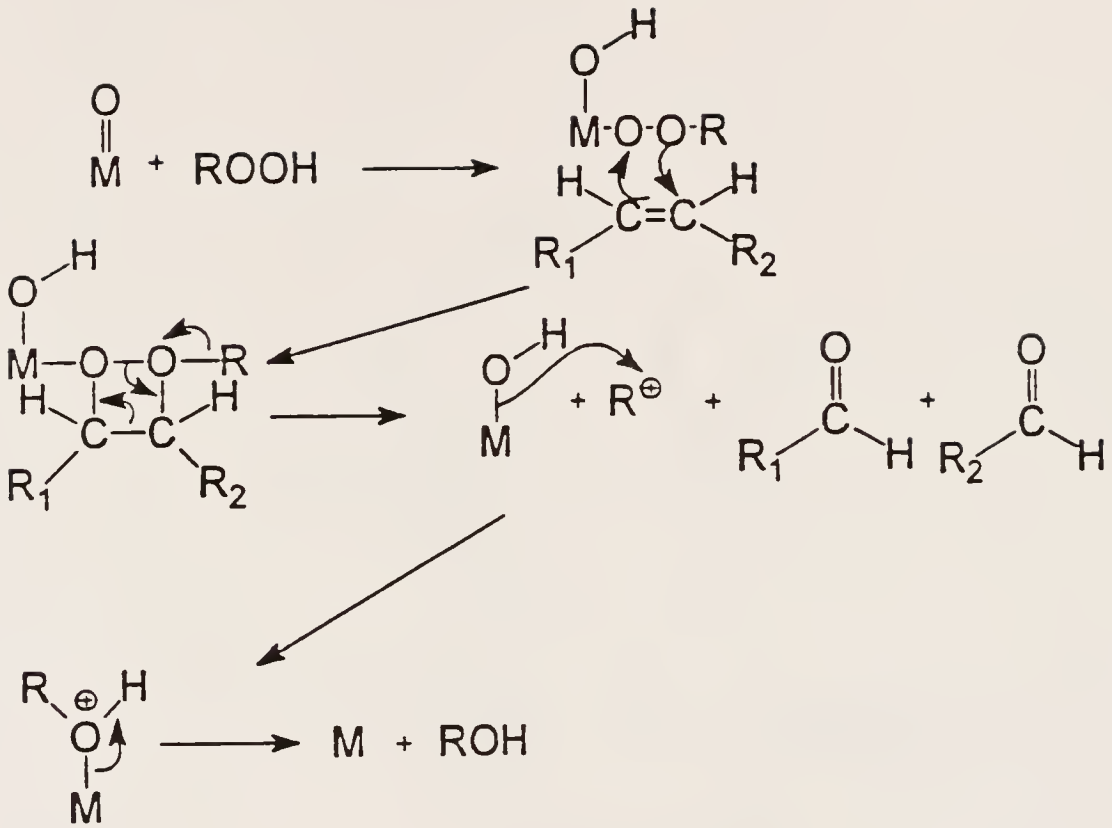


Figure 3-16 Benzaldehyde Formation in Polar Solvents.

peroxymetallocycle by an alkylperoxo anion (Figure 3-17). The reaction conditions would seem to suggest that this pathway is likely. Also, in the presence of a base, such as pyridine, and/or excess t-butyl hydroperoxide, the reaction would be expected to show an increase in the amount of benzaldehyde if the reaction is second order in t-butyl hydroperoxide. Looking at the results for the molybdenum-catalyzed oxidation of cis- and trans-β-methylstyrene, an increase in the oxidant to substrate molar ratio and/or the addition of pyridine showed no increase in the amount of benzaldehyde (Tables 3-19 and 3-20). The addition of pyridine to these reactions could possibly accelerate the epoxide formation pathway. These experimental results seem to suggest that the formation of benzaldehyde in these systems does not occur via this type of mechanism.

The formation of epoxide was more pronounced for trans-β-methylstyrene than for the cis analog. As a result of the low selectivity to epoxide seen for the oxidation of cis-β-methylstyrene, several experiments were performed using styrene as the substrate. An even lower selectivity to epoxide was observed for this substrate in both CCl_4 and 1-methyl-2-pyrrolidinone (Table 3-21). The addition of a catalytic amount of pyridine to the reactions resulted in an increase and a decrease in the formation of epoxide and benzaldehyde, respectively. As mentioned earlier, the

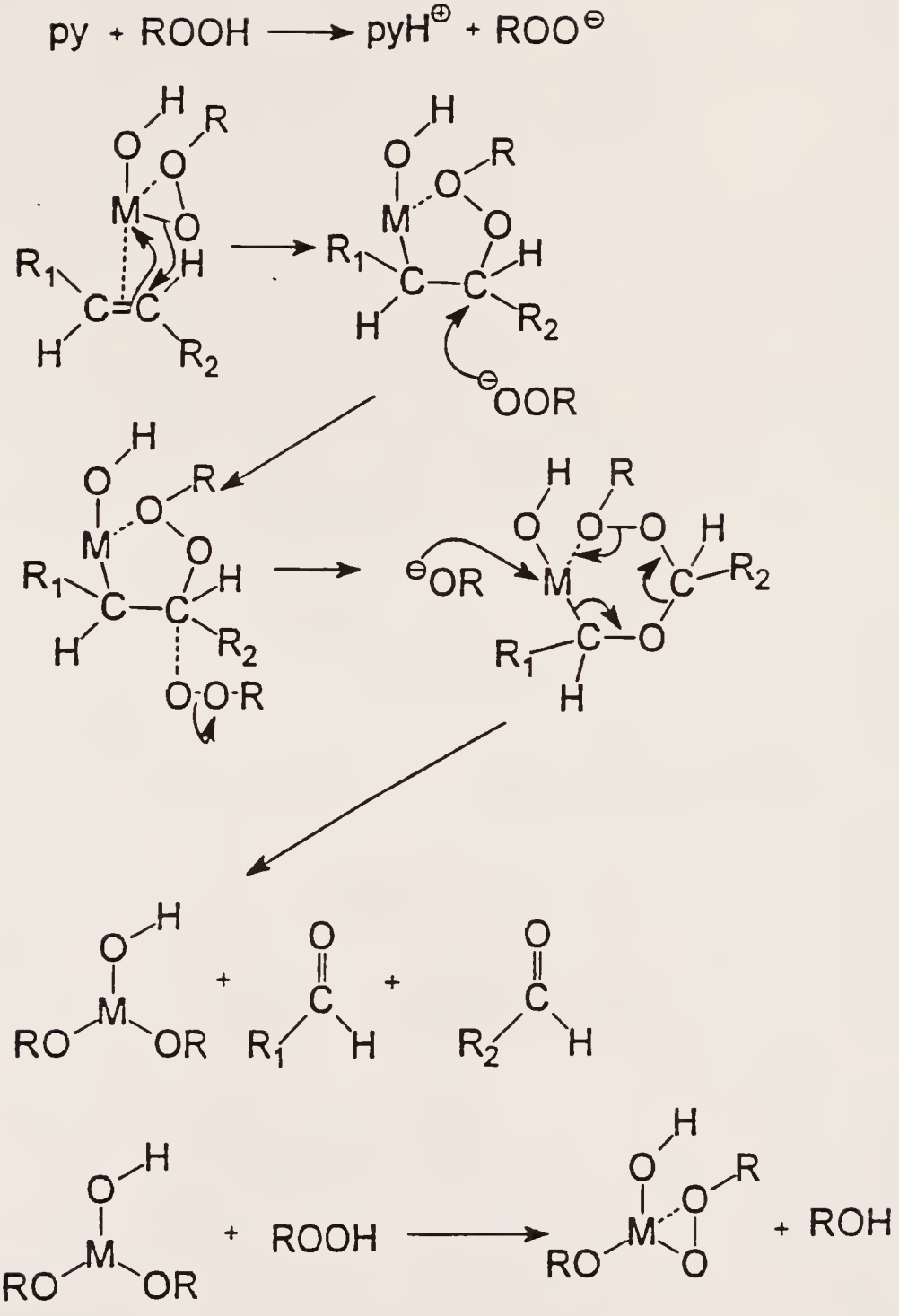


Figure 3-17 Benzaldehyde Formation by a Baeyer-Villiger-Type Mechanism.

Table 3-19 Effect of Excess t-Butyl Hydroperoxide on cis-β-Methylstyrene Oxidation.

Solvent	O/S	Pyridine	E/B
CCl_4	1:1	No	1:2
CCl_4	1:1	Yes	3:1
CCl_4	2:1	No	1:2
CCl_4	2:1	Yes	3.2:1
NMP	1:1	No	1:7
NMP	1:1	Yes	1:3
NMP	2:1	No	1:6
NMP	2:1	Yes	1:4

Note: Reaction conditions:
substrate (2.3×10^{-2} moles)
catalyst (2.3×10^{-5} moles, $Mo(O)_2(acac)_2$)
solvent (47 mL)
t-BuOOH (2.3×10^{-2} moles for 1:1)
pyridine (2.3×10^{-5} moles, if added)
run under N_2 at 75°C for 48 hours.

Table 3-20 Effect of Excess t-Butyl Hydroperoxide on trans-β-Methylstyrene Oxidation.

Solvent	O/S	Pyridine	E/B
CCl_4	1:1	No	10:1
CCl_4	1:1	Yes	24:1
CCl_4	2:1	No	11:1
CCl_4	2:1	Yes	22:1
NMP	1:1	No	1:2
NMP	1:1	Yes	2.2:1
NMP	2:1	No	1:2
NMP	2:1	Yes	3:1

Note: Reaction conditions:
substrate (2.3×10^{-2} moles)
catalyst (2.3×10^{-5} moles, $Mo(O)_2(acac)_2$)
solvent (47 mL)
t-BuOOH (2.3×10^{-2} moles for 2:1)
pyridine (2.3×10^{-5} moles, if added)
run under N_2 at 75°C for 48 hours.

Table 3-21 Styrene Oxidation.

Solvent	Pyridine	E/B
CCl_4	No	1:4
CCl_4	Yes	1:1
NMP	No	1:9
NMP	Yes	1:5

Note: Reaction conditions:
substrate (2.3×10^{-2} moles)
catalyst (2.3×10^{-5} moles, $Mo(O)_2(acac)_2$)
pyridine (2.3×10^{-5} moles, if added)
t-BuOOH (2.3×10^{-2} moles)
run under N_2 at 75°C for 48 hours.

dissociation of the metal-bound epoxide is probably facilitated by the facile coordination of the pyridine in the metal-containing intermediate.

1-Hexene Oxidation

As a result of the high selectivity to epoxide observed in the oxidation of the substituted olefin, trans-β-methylstyrene, an investigation into the use of the in situ generated 5-hydroperoxo-1-methyl-2-pyrrolidinone was pursued using the terminal, unfunctionalized olefin, 1-hexene, in the presence of various transition metal catalysts (Table 3-22). Looking at the results for the homogeneous oxidation of 1-hexene, the reactions were selective to epoxide formation. Even though the yields were low, thise metal catalysts possessing Class IVa[26,27] behavior gave the higher yields. In these reactions, a large amount of O_2 uptake and subsequent hydroperoxide decomposition was observed.

Using the more efficient epoxidation catalyst, $Mo(O)_2(acac)_2$ (Class IVb),[26,27] several attempts were made to determine if an increase in the reaction temperature was necessary to overcome a possible activation barrier. An increase in the yield of epoxide was observed for a 25°C temperature increase (Tables 3-22 and 3-23). Substitution of the pre-generated N-alkylamide hydroperoxide for the in situ generated hydroperoxide gave a similar result.

Looking at Tables 3-22 and 3-24, no substrate oxidation was observed with the catalyst, $[Ru(dmp)_2(H_2O)_2][PF_6]_2$, in the

Table 3-22 1-Hexene Epoxidation in 1-Methyl-2-pyrrolidinone.

Catalyst	Products (%)
Blank	0 (96 hours)
$CoCl_2 \cdot 6H_2O$	epoxide (2.0) (24 hours)
$Co(octoate)_2$	epoxide (4.6) (24 hours)
$Co(hfacac)_2 \cdot 2DMF$	epoxide (2.0) (24 hours)
$Ti(O^iPr)_4$	epoxide (<1) (48 hours)
$V(O)(acac)_2$	epoxide (2.2) (48 hours)
$Mo(O)_2(acac)_2$	epoxide (<1) (48 hours)
$RuCl_3 \cdot 3H_2O$	epoxide (4.0) (24 hours)
$[Ru(dmp)_2(H_2O)_2][PF_6]_2$	0 (48 hours)

Note: Reaction conditions:
substrate (4.0×10^{-2} moles)
catalyst (4.0×10^{-4} moles)
solvent (NMP, 45 mL)
run under O_2 (50 psig) at 75°C.
Completion times are given in parenthesis.

Table 3-23 1-Hexene Epoxidation Using $Mo(O)_2(acac)_2$.

Catalyst	Hydroperoxide	Products (%)
$Mo(O)_2(acac)_2$	in-situ	epoxide (2.3)
$Mo(O)_2(acac)_2$	pre-generated	epoxide (2.5)

Note: Reaction conditions:
substrate (4.0×10^{-2} moles)
catalyst (4.0×10^{-4} moles)
solvent (NMP, 45 mL)
run under O_2 (50 psig) at 100°C for 48 hours.

Table 3-24 1-Hexene Epoxidation Using $[Ru(dmp)_2(H_2O)_2][PF_6]_2$.

Catalyst	Products (%)
$[Ru(dmp)_2(H_2O)_2][PF_6]_2$	0
$[Ru(dmp)_2(H_2O)_2][PF_6]_2$ (with H_2O_2)	epoxide (<1)

Note: Reaction conditions:
substrate (4.0×10^{-2} moles)
catalyst (4.0×10^{-4} moles)
solvent (NMP, 45 mL)
H_2O_2 (4.7×10^{-4} moles)
run under O_2 (50 psig) at 100°C for 48 hours.

in situ 5-hydroperoxo-1-methyl-2-pyrrolidinone system at both 75 and 100°C. As in the case of the oxidation of trans-β-methylstyrene, the Class IVa[26,27] component of this catalyst led to an elimination of the induction period by a metal-catalyzed radical-chain mechanism. The formation of the Ru(IV)(O) and the $Ru(VI)(O)_2$ species was signaled by an observed color change from purple-red to yellow.[118] Although no oxidation of the unfunctionalized olefin was observed, a large amount of O_2 uptake and subsequent hydroperoxide decomposition to N-methylsuccinimide occurred. The addition of 30% H_2O_2 to an analogous reaction at 100°C led to a very low yield of epoxide being observed (Table 3-24).

The O_2 utilization data for the homogeneous cobalt(II)-catalyzed epoxidations of 1-hexene show that the rapid hydroperoxide decomposition was a major problem (Table 3-25). For this reason, the utilization of metal ion-exchanged zeolites were evaluated as potential catalysts in the oxidation of 1-hexene. Earlier work in our laboratory[17] demonstrated that a CoNa-Y zeolite catalyst increases the formation of the N-alkylamide hydroperoxide from NMP without the hydroperoxide decomposition (Class IVa)[26,27] observed for various homogeneous transition metal catalysts.

Looking at Table 3-26, no increase in the amount of epoxide was observed after 24 hours using CoNa-Y as the catalyst. Iodometric titrations of the filtered reaction mixture showed an approximate 2M concentration of the in situ generated alkyl hydroperoxide; thus, indicating no rapid

Table 3-25 O_2 Utilization in 1-Hexene Epoxidation.

Catalyst	Moles O_2/Moles Epoxide
$CoCl_2 \cdot 6H_2O$	47.3/1.0
$Co(octoate)_2$	42.7/1.0

Note: Reaction conditions:
substrate (4.0×10^{-2} moles)
catalyst (4.0×10^{-4} moles)
solvent (NMP, 45 mL)
run under O_2 (50 psig) at 75°C.

Table 3-26 1-Hexene Epoxidation Using Heterogeneous Cobalt Catalyst.

Catalyst	Products (%)
none	none
$CoCl_2 \cdot 6H_2O$	epoxide (2.0)
CoNa-Y[a]	epoxide (4.6)
Co(dmp)Na-Y[a]	epoxide (14)

Note: Reaction conditions:
catalyst (4.0×10^{-4} moles)
substrate (4.0×10^{-2} moles)
NMP (4.8×10^{-1} moles)
run under O_2 (50 psig) at 75°C for 24 hours.

a. These heterogeneous catalysts give a lesser amount of hydroperoxide decomposition.

hydroperoxide decomposition taking place. The use of a cobalt complex possessing the 2,9-dimethyl-1,10-phenanthrolene ligand inside of the zeolite cages led to an increase in the amount of epoxide formed and no observed rapid hydroperoxide decomposition.

Experimental

Reagents and Equipment

1-Methyl-2-pyrrolidinone (HPLC Grade), t-butyl hydroperoxide (90% solution), and cis- and trans-β-methylstyrenes were obtained from Aldrich Chemical Company and were used as received. Styrene was obtained from Aldrich Chemical Company and was vacuum distilled prior to use. Lancaster Synthesis supplied the 1,2-epoxyhexane, 1-hexen-3-ol, and 1-hexen-3-one. The cyclohexene and 1-hexene were obtained from Aldrich Chemical Company and were passed through an activated alumina column to remove any impurities. The metal complexes, $Mo(O)_2(acac)_2$, $V(O)(acac)_2$, $RuCl_3 \cdot 3H_2O$, and $Ti(O^iPr)_4$ were received from Aldrich Chemical Company and were used as received. Mooney Chemicals, Inc. supplied the $Co(octoate)_2$ (12% Co by weight in mineral spirits). All other reagents and solvents were obtained from Fischer Scientific and were used as received.

The epoxides, cis-1-phenylpropylene oxide and trans-1-phenylpropylene oxide were prepared by literature methods.[127,128]

$Co(hfacac)_2 \cdot 2DMF$ and $[Ru(dmp)_2(H_2O)_2][PF_6]_2$ were prepared by previously reported literature methods.[36,129]

The heterogeneous catalysts, CoNa-Y and Co(dmp)-Y, were prepared by literature methods.[24,25]

A Varian 3700 GC with an FID and Hewlett Packard 2290A integrator was used to analyze the oxidation reactions, using a 6 foot stainless steel column packed with DEGS (15%) on Chromosorb W(80/100 mesh). All reactants and products were indentified and quantified, using known standards.

^1H and ^{13}C NMR spectra were run on a General Electric QE-300 Fourier Transform Spectrometer operated at 300MHz and 75MHz, respectively. The samples were run in d_6-benzene or d_1-chloroform with Me_4Si as an internal reference.

Ultraviolet and visible spectra were recorded on a Perkin-Elmer 330 spectrophotometer in 1 cm path length quartz cells.

All reactions were run in a Parr Pressure Apparatus at the indicated temperature and pressure.

CAUTION! Extreme care should be taken when working with a pressurized apparatus at or above room temperature. Appropriate shields must be used and fire extinguishers should be nearby. For elevated temperatures, the reaction solution should be cooled to room temperature before disassembling the pressure apparatus.

Peroxide concentrations were measured by removing 0.5-2.0 mL samples from the pressure bottles with a 12 in. stainless steel needle. The iodometric titration was performed immediately.[33]

CAUTION! Many hydroperoxides are shock/temperature sensitive and should be treated as potentially explosive.

Cyclohexene Oxidations

1-Methyl-2-pyrrolidinone (47 mL), cyclohexene (2.5g, 3.1mL, $3.0x10^{-2}$ moles), and the appropriate catalyst ($3.0x10^{-5}$ moles, see Table 3-3) were placed in a 250 mL Parr Pressure Bottle equiped with magnetic stirring. After the pressure apparatus was assembled, the reactor was purged 3 times with O_2 (50 psig) and then pressurized with O_2 (50 psig). The reactor was placed in a 75°C oil bath. Recharging with O_2 (50 psig) was performed as needed. Samples were drawn periodically and analyzed by GC.

trans-β-Methylstyrene Oxidations

1-Methyl-2-pyrrolidinone (47 mL), trans-β-methylstyrene (2.7g, 3.0mL, $2.3x10^{-2}$ moles), and the appropriate catalyst ($2.3x10^{-5}$ moles, see Table 3-4) were placed in a 250 mL Parr Pressure Bottle equipped with magnetic stirring. After the pressure apparatus was assembled, the reactor was purged 3 times with O_2 (50 psig) and then pressurized with O_2 (50 psig). The reactor was placed in a 75°C oil bath. Recharging

with O_2 (50 psig) was performed as needed. Samples were drawn periodically and analyzed by GC.

cis-β-Methylstyrene Oxidations

1-Methyl-2-pyrrolidinone (47 mL), cis-β-methylstyrene (2.7g, 3.0mL, $2.3x10^{-2}$ moles), and the appropriate catalyst ($2.3x10^{-5}$ moles, see Table 3-5) were placed in a 250 mL Parr Pressure Bottle equipped with magnetic stirring. After the pressure apparatus was assembled, the reactor was purged 3 times with O_2 (50 psig) and then pressurized with O_2 (50 psig). The reactor was placed in a 75°C oil bath. Recharging with O_2 (50 psig) was performed as needed. Samples were drawn periodically and analyzed by GC.

Solvent Effects

The appropriate catalyst, oxidant, solvent, and substrate (see Tables 3-6 and 3-7) were placed in a 250 mL Parr Pressure Bottle equipped with magnetic stirring. After the pressure apparatus was assembled, the reactor was purged 3 times with the appropriate atmosphere (see Tables 3-6 and 3-7) and then pressurized with the appropriate atmosphere. The reactor was placed in a 75°C oil bath. Recharging with the appropriate atmosphere was performed as needed. Samples were drawn periodically and analyzed by GC.

Halocarbon Addition

The appropriate catalyst, halocarbon, oxidant, solvent, and substrate (Table 3-8) were placed in a 250 mL Parr Pressure Bottle equipped with magnetic stirring. After the pressure apparatus was assembled, the reactor was purged 3 times with the appropriate atmosphere (see Table 3-8) and then pressurized with the appropriate atmosphere. The reactor was placed in a 75°C oil bath. Recharging with the appropriate atmosphere was performed as needed. Samples were drawn periodically and analyzed by ^{1}H and ^{13}C NMR and GC.

Effects of Added Pyridine

The appropriate catalyst, oxidant, solvent, and substrate (see Tables 3-9, 3-10, 3-11, and 3-12) were placed in a 250 mL Parr Pressure Bottle equipped with magnetic stirring. Pyridine (or pyridine-N-oxide)(2.3×10^{-5} moles) was added to the reaction solution. After the pressure apparatus was assembled, the reactor was purged 3 times with the appropriate atmosphere (see Tables 3-9, 3-10, 3-11, and 3-12) and then pressurized with the appropriate atmosphere. The reactor was placed in a 75°C oil bath. Recharging with the appropriate atmosphere was performed as needed. Samples were drawn periodically and analyzed by GC.

Pyridine Oxidations

Pyridine (1.0×10^{-1} moles) and the appropriate catalyst, oxidant, and solvent (see Table 3-13) were placed in a 250 mL

Parr Pressure Bottle equipped with magnetic stirring. After the pressure apparatus was assembled, the reactor was purged 3 times with the appropriate atmosphere (see Table 3-13) and then pressurized with the appropriate atmosphere. The reactor was placed in a 75°C oil bath. Recharging with the appropriate atmosphere was performed as needed. Samples were drawn periodically and analyzed by ^{1}H and ^{13}C NMR.

trans-β-Methylstyrene Oxidations Using Pyridine-N-oxide

The appropriate catalyst, solvent (see Table 3-14), trans-β-methylstyrene (2.7g, 3.0mL, $2.3x10^{-2}$ moles), and pyridine-N-oxide (2.2g, $2.3x10^{-2}$ moles) were placed in a 250 mL Parr Pressure Bottle equipped with magnetic stirring. After the pressure apparatus was assembled, the reactor was purged 3 times with N_2 (10 psig) and then pressurized with N_2 (10 psig). The reactor was placed in a 75°C oil bath. Recharging with N_2 (10 psig) was performed as needed. Samples were drawn periodically and analyzed by GC.

Olefin Oxidations Using Substituted Pyridines

The appropriate catalyst, oxidant, solvent, and substrate (see Tables 3-15 and 3-16) were placed in a 250 mL Parr Pressure Bottle equipped with magnetic stirring. The appropriate substituted pyridine ($2.3x10^{-5}$ moles) was added to the reaction solution. After the pressure apparatus was assembled, the reactor was purged 3 times with N_2 (10 psig) and then pressurized with N_2 (10 psig). The reactor was

placed in a 75°C oil bath. Recharging with N_2 (10 psig) was performed as needed. Samples were drawn periodically and analyzed by GC.

^{1}H NMR Study of $Mo(O)_2(acac)_2$/t-Butyl Hydroperoxide Reaction

$Mo(O)_2(acac)_2$ (0.652g, $2.0x10^{-3}$ moles) and the appropriate solvent (20 mL) (see Table 3-17) were placed in a 100 mL round bottom flask equipped with magnetic stirring and an N_2 atmosphere. After dissolution of the solid, t-butyl hydroperoxide (0.9 mL of a 90% solution, $8.0x10^{-3}$ moles) was added to the reaction solution. Samples were drawn periodically and analyzed by ^{1}H NMR.

cis- and trans-β-Methylstyrene Oxidations in $CHCl_3$ and CCl_4

These reactions were run, using the appropriate aromatic amine, catalyst, oxidant, solvent, and substrate (see Table 3-18), by the method described in the Olefin Oxidations Using Substituted Pyridines section.

Effect of Excess t-Butyl Hydroperoxide

These reactions were run, using the appropriate aromatic amine, catalyst, oxidant, solvent, and substrate (see Tables 3-19 and 3-20), by the method described in the Olefin Oxidations Using Substituted Pyridines section.

Styrene Oxidation

These reactions were run, using the appropriate aromatic amine, catalyst, oxidant, solvent, and substrate (see Table 3-21), by the method described in the Olefin Oxidations Using Substituted Pyridines section.

1-Hexene Oxidations

1-Methyl-2-pyrrolidinone (45 mL), 1-hexene (3.4g, 5.0mL, $4.0x10^{-2}$ moles), and the appropriate catalyst ($4.0x10^{-4}$ moles) (see Tables 3-22, 3-23, 3-24, 3-25, and 3-26) were placed in a 250 mL Parr Pressure Bottle equipped with magnetic stirring. After the pressure apparatus was assembled, the reactor was purged 3 times with O_2 (50 psig) and then pressurized with O_2 (50 psig). The reactor was placed in an oil bath of the appropriate temperature (see Tables 3-22, 3-23, 3-24, 3-25, 3-26). Recharging with O_2 (50 psig) was performed as needed. Samples were drawn periodically and analyzed by GC.

Conclusions

In the presence of transition metal complexes, alkenes, such as trans-β-methylstyrene and 1-hexene, can be selectively oxidized to the corresponding epoxides under mild conditions (O_2 (50 psig) at 75°C) in the solvent, 1-methyl-2-pyrrolidinone. When reacted with molecular oxygen at 75°C, 1-methyl-2-pyrrolidinone is converted to the corresponding N-alkylamide hydroperoxide, which oxidized the olefinic substrate to the corresponding oxidation products in the

presence of transition metal catalysts. Both the completion times and the product selectivities are dependent on the nature of the transition metal catalysts. Higher selectivity to epoxide formation and less efficient utilization of the alkyl hydroperoxide are observed with radical-chain catalysts (Class IVa).[26,27] The use of metal oxo complexes results in a substantial lowering of the selectivity to epoxide. Lower stereoselectivity in the formation of epoxide is exhibited in these catalytic systems.

The oxidation of cyclohexene by this oxidative system favors the formation of the allylic products that result from the autoxidation of the substrate. The more facile autoxidation process predominates over the formation of the N-alkylamide hydroperoxide, which is the active oxidant for epoxide formation.

Further investigations into the $Mo(O)_2(acac)_2$-catalyzed oxidations of cis- and trans-β-methylstyrene have shown that this metal complex behaves in a Class IVb[26,27] manner. The stereoselectivity in the formation of epoxides in this system exhibited a pronounced dependency on the polarity of the solvent used. Using t-butyl hydroperoxide, high stereoselectivity in the formation of epoxide was observed with this metal complex in non-polar solvents. On the other hand, the use of pre-generated 5-hydroperoxo-1-methyl-2-pyrrolidinone, or t-butyl hydroperoxide in the oxidation of cis-β-methylstyrene exhibited low stereoselectivities in epoxide formation in the polar solvent, 1-methyl-2-pyrrolidinone.

Spectroscopic evidence supports the involvement of a more selective triangular metal alkylperoxo species and a less selective linear metal alkylperoxo species in non-polar and polar solvents, respectively.

The addition of a catalytic amount of pyridine to the molybdenum-catalyzed oxidations of cis- and trans-β-methylstyrene resulted in the increased formation of the corresponding epoxides. It is thought that the pyridine facilitates the dissociation of the epoxide from the metal intermediate via facile coordination to the molybdenum center.

Further suggested work in this area would involve the synthesis and utilization of chiral transition metal complexes that can function in a Class IV[26,27] manner to form alkyl hydroperoxides from N-alkylamides, such as 1-methyl-2-pyrrolidinone and 1,5-dimethyl-2-pyrrolidinone, and then function in a Class IVb[26,27] manner to perform enantioselective oxidations of prochiral alkenes. Also, the oxidation of alkenes by a chiral alkyl hydroperoxide may produce results similar to the results observed by Sharpless and co-workers without the complications caused by unstable chiral transition metal complexes.[83]

CHAPTER 4
TRANSITION METAL-CATALYZED OXIDATIONS OF THIOETHERS IN 1-METHYL-2-PYRROLIDINONE SOLVENT

Introduction

The oxidation of thioethers to give the corresponding sulfoxides and sulfones, employing transition metal complexes as catalysts, has received considerable attention with much of this interest occurring for a variety of reasons. These include the development of a selective scheme for the synthesis of the oxygenated products which are of greater utility,[130] the use of thioethers as probe molecules in mechanistic studies due to their similar reactivity to olefins in epoxidation reactions,[131] an interest in the pathways by which sulfides are oxidized,[132] and their use as substrates for stereoselective oxidations.[133] In recent years, catalytic thioether oxidations have been receiving an increasing amount of attention in the development of safer methods for the destruction of chemical weapons, such as mustard.[134] The transition metal-catalyzed thioether oxidations presented in this work are classified according to the classification scheme reported by Drago and Beer[26] and Drago[27] which is described in the previous chapter.

One approach to the oxidation of thioethers involves the use of molecular oxygen as the primary oxidant with and without transition metal complexes.[135] Bateman and Cunneen studied the reactivity of a variety of thioethers with molecular oxygen at temperatures between 45 and 75°C and in the presence of various catalysts.[136] Even though the unsaturated sulfides reacted readily with molecular oxygen at 75°C, the saturated sulfides, such as n-butyl sulfide, absorbed no oxygen during a 24 hour period in the absence of a radical initiator. These studies of the autoxidations of various saturated and unsaturated thioethers have led to the conclusion that the autoxidation of the unsaturated sulfides occurs primarily by abstraction of the α-hydrogen and that the sulfoxides are produced in low yields by reaction of the unreacted thioethers with the intermediate α-hydroperoxides.[137,138] The saturated thioethers were found to be fairly inert toward autoxidation in the absence of an initiator.

Correa and Riley reported the reaction of several saturated thioethers with molecular oxygen at or above 100°C in polar solvents.[139] While these autoxidations did not occur in solvents of low polarity, the use of polar solvents, such as H_2O and lower alcohols, resulted in high conversions of the aliphatic thioethers to the corresponding sulfoxides. In addition to the elevated temperatures required, the dependence on solvent polarity are suggestive of an initial reversible endothermic one-electron transfer from the thioether to the

oxygen (Figure 4-1). The observed sulfoxide products can be explained by the reduction of the oxygenated radical cation to a zwitterion with either superoxide or another molecule of the thioether, generating a chain reaction. Reaction of the zwitterion with the thioether would result in the formation of two molecules of sulfoxide.

Further work by Riley and Correa demonstrated that the addition of a catalytic amount of the cerium(IV) salt, $(NH_4)_2Ce(NO_3)_6$, to these thioether autoxidations greatly enhances the oxidation rate when compared to the uncatalyzed thioether oxidations.[130,140] While the uncatalyzed autoxidation involves an initial unfavorable electron transfer to oxygen, the use of cerium(IV) salts was found to facilitate the electron transfer to yield the radical cation. Oxygenation of the radical cation results in oxygenated radical cation which reoxidizes cerium(III) to cerium(IV) in a Class V (metal-centered oxidizing agent) manner.[26,27] The resulting zwitterionic intermediate reacts with the thioether to form two molecules of sulfoxide.

The oxidation of sulfides of different structure has been carried in the presence of neutral ruthenium(II) complexes of the type cis- or trans-$RuX_2(Me_2SO)_4$ (where X=Cl or Br) in methanol or isopropanol solvents, with total conversion of the sulfide to the corresponding sulfoxide and sulfone being observed.[141,142] The observed reaction rates at 100°C under O_2 (100 psig) are much faster than the reported rates for other metal catalysts, such as $RuCl_3$ or $RuCl_2(PPh_3)_3$.[143] The

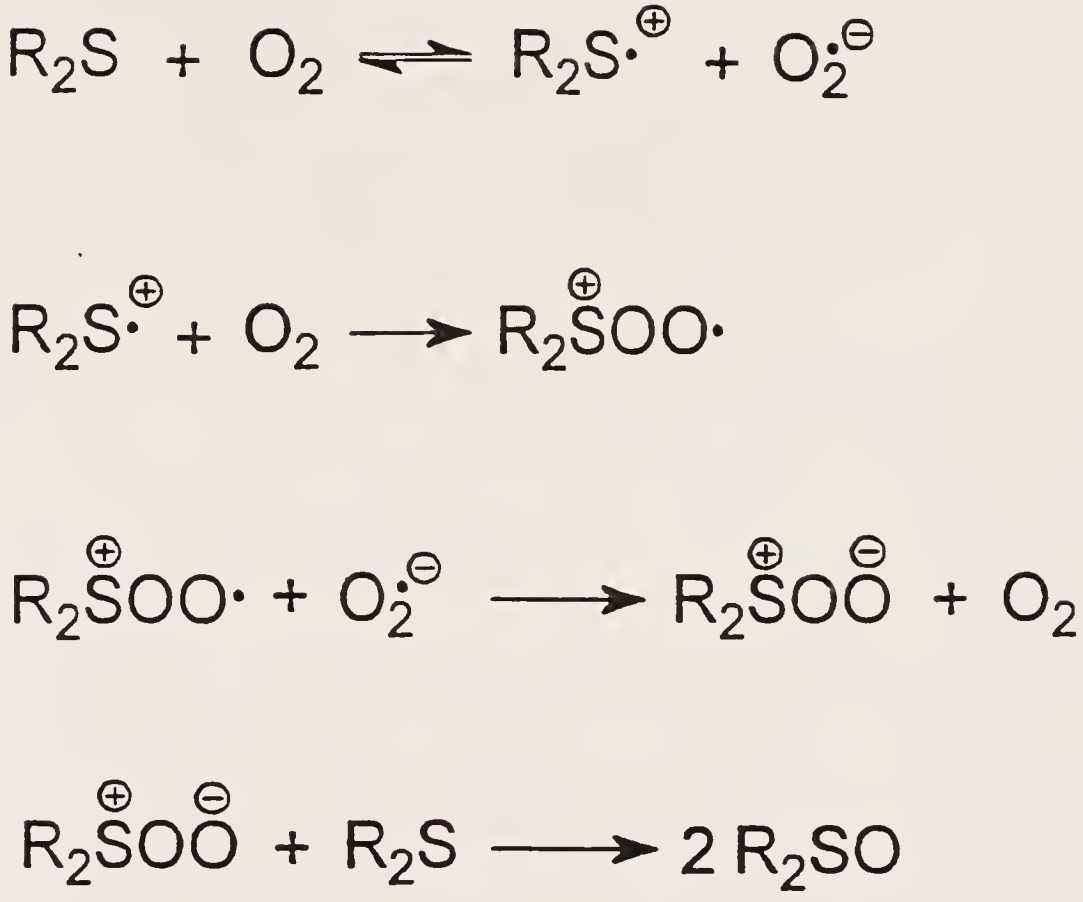
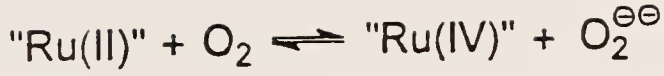


Figure 4-1 Selective Molecular Oxygen Oxidation of Thioethers.[139]

reaction rate increases with increasing concentrations of catalyst, alcohol, and oxygen, and is independent of the concentration of sulfide.[141,142] A mechanism involving a two-electron oxidation of the ruthenium(II) complex to a ruthenium(IV) species by molecular oxygen has been proposed (Figure 4-2). The simultaneous formation of peroxide occurs with the peroxide functioning as the active sulfide oxidant. The alcohol solvent takes part in the catalyst regeneration; thus completing the catalytic cycle. In a later study, Oliver and Riley suggested that the active catalytic species in the thioether oxidations were mixed sulfide and sulfoxide complexes of the general formula, $RuX_2(SR_2)_2(Me_2SO)_2$.[144-146] It is interesting to note that the proposed mechanism for this catalytic reaction does not appear to fit any of the five classes in the classification acheme, although the reaction is likely to involve some Class IV behavior.[26,27]

Another method for the oxidation of thioethers involves the use of hydroperoxy compounds, such as alkyl hydroperoxides or H_2O_2, as oxidants. Even though thioethers can be oxidized in the absence of transition metal catalyst using H_2O_2[147,148] or t-butyl hydroperoxide (t-BuOOH),[148-152] low product yields and poor selectivities result. Schultz et al. reported that the oxidation of 2-hydroxyethyl sulfides using an excess of 30-35% H_2O_2 in H_2O alone without a catalyst required elevated temperatures and long reaction times.[153] Poor yields of the corresponding sulfone resulted. These investigators eventually developed an aqueous oxidative system using several



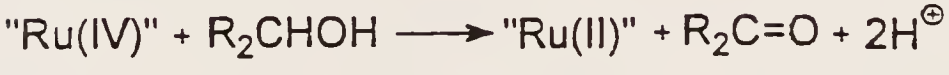


Figure 4-2 Mechanism for $RuX_2(Me_2SO)_4$ Catalyzed Sulfide Oxidations.[141,142]

molybdenum, tungsten, and vanadium compounds as catalysts.[153-156] Reportedly, the starting sulfide can contain, in addition to hydroxyl groups, a variety of other functional groups which are not attacked.

Using a catalytic amount of V_2O_5, sulfides have been oxidized with an anhydrous solution of H_2O_2 in t-butyl alcohol to give the corresponding sulfoxides and sulfones.[157,158] For example, the oxidation of diphenyl sulfide using this catalyst gave a quantitative yield of diphenyl sulfone.[158] The oxidation of diphenyl sulfide by H_2O_2 in the presence of a catalytic amount of $NaVO_3$ is suggested to occur via a diperoxyvanadate at lower catalyst concentrations;[159] thus, exhibiting Class IVb behavior.[26,27]

The $V(O)(acac)_2$-catalyzed oxidations of thioethers have been extensively studied by Modena and co-workers using H_2O_2 as the oxidant.[160,161,162] The oxidation of p-chlorophenyl methyl sulfide with H_2O_2 in the presence of the vanadium(IV) complex in dioxane and dioxane-ethanol resulted in a quantitative yield of the corresponding sulfoxide.[161] The active oxidizing agent was suggested to be a side-on bonded monoperoxo vanadium species. These catalytic systems can be envisigned as occurring by a nucleophilic attack on a metal-bound peroxo species (Class IVb).[26,27] The vanadium catalysts also decompose the oxidant by a radical mechanism (Class IVa).[26,27]

Metal catalysis by molybdenum(VI) and tungsten(VI) complexes in the oxidation of thioethers has received a great

deal of attention using H_2O_2 as the oxidant.[162-167] In one study, the oxidation of p-chlorophenyl methyl sulfide in the presence of catalytic amounts of three molybdenum complexes, $Mo(O)_2(acac)_2$, $Mo(CO)_6$, and $MoO_5 \cdot HMPT \cdot H_2O$ was investigated in ethanol. These reactions afforded quantitative yields of the corresponding sulfoxide.[164] The catalytic efficiency of the three molybdenum species employed was not affected by the nature of the original ligand environment of the molybdenum species added, nor by their initial oxidation states. The oxidizing agent formed in solution was suggested to be the peroxo complex $MoO_5(EtOH)_2$. The observed reactivity order of substrates of differing nucleophilicity (sulfides > sulfoxides > alkenes) strongly supports the transfer of an electrophilic oxygen of the metal peroxo species to the substrate.[163] Analogous results were obtained using the tungsten(VI) complexes, $WO_5 \cdot HMPT \cdot H_2O$ and $W(CO)_6$.[162] These molybdenum- and tungsten-catalyzed oxidations proceed by a Class IVb type of mechanism.[26,27]

Bortolini et al. reported the oxidation of several thioethers using H_2O_2 in the presence of $Ti(O)(acac)_2$ in ethanol at 25°C.[168] The small inhibitory effect of added acetylacetonate on the oxidation rate suggested that the ligand does not compete effectively with H_2O_2 for coordination sites on the titanium(IV) and was therefore removed via solvolysis of the metal complex. The reaction of the resulting titanyl alkoxide complex with H_2O_2 results in the

formation of a side-bonded peroxotitanium(IV) species. This active metal peroxo species oxidizes the thioether in a Class IVb manner.[26,27]

The oxidation of thioethers by anhydrous H_2O_2 was reported using catalytic amounts of iron(II) and iron(III) catalysts in a non-complexing solvent.[169-171] The oxidations of diphenyl sulfide and diphenylsulfoxide using this oxidative system led to the complete conversion of the substrate to the corresponding sulfoxide and sulfone, respectively.[170] A 58-60% efficiency in the use of H_2O_2 was observed in these reactions (Class IVa).[26,27]

The metal complex, $[Fe(CH_3CN)_4][ClO_4]_2$, catalyzed the oxidations of diphenyl sulfide and diphenyl sulfoxide with hydroperoxide efficiencies of 1-7% using t-butyl hydroperoxide as the oxidant.[171] These oxidations activate peroxides in a Class IVa manner.[26,27]

The molybdenum- and vanadium-catalyzed oxidations of thioethers has been extensively studied using t-butyl hydroperoxide as the oxidant.[131,162,172-175] The reaction of n-butyl sulfide with t-butyl hydroperoxide in ethanol at 25°C in the presence of a catalytic amount of $V(O)(acac)_2$ results in a quantitative yield of n-butyl sulfoxide.[172] Nucleophilic attack by the sulfide on the oxygen-oxygen bond of a vanadium alkylperoxo species is suggested (Class IVb).[26,27] In alcoholic solvents and in the presence of t-butyl hydroperoxide, $V(O)(acac)_2$ is converted into the corresponding vanadate esters, $V(O)(OR)_3$, as a result of the dissociation of

the acetylacetonate ligands. Oxidation of the initial vanadium(IV) complex to the corresponding vanadium(V) species occurs.

Other reports by Modena and co-workers describe the employment of $Mo(O)_2(acac)_2$ in the oxidations of several different sulfides.[162,175] For instance, the molybdenum-catalyzed oxidation of n-butyl sulfide by t-butyl hydroperoxide afforded a quantitative yield of the corresponding sulfoxide at 25°C in dry ethanol.[175] The suggested mechanism for these metal-catalyzed sulfoxidations involves a nucleophilic attack of the substrate on the electrophilic oxygen of the metal alkylperoxo species. (Class IVb).[26,27]

The catalytic activity of $Ti(O)(acac)_2$ and $Ti(O^iPr)_4$ were investigated in toluene solvent using t-butyl hydroperoxide in the oxidation of n-butyl sulfide and p-chlorophenyl methyl sulfide.[176] The reactions afforded quantitative yields of the corresponding sulfoxides. Based on the experimental data, the mechanism was suggested to involve the nucleophilic attack of the substrate on the metal-bound peroxide species (Class IVb).[26,27]

In the presence of t-butyl hydroperoxide, polymer-supported catalysts containing high-valent molybdenum and vanadium species have been used to oxidize n-butyl sulfide and dimethylsulfoxide to n-butyl sulfoxide and dimethylsulfone, respectively.[177,178] When the polymer-supported complex is recycled and reused, lower product yields result due to the loss of metal ions.

The occurence of chiral sulfoxides with a defined stereochemistry at the sulfur atom in some drugs and natural products has led to an interest in the transition metal-catalyzed asymmetric oxidation of thioethers using alkyl hydroperoxides as oxidants.[179,180]

When the well-known Sharpless reagent for asymmetric epoxidations was modified by the addition of one molar equivalent of H_2O, the resulting reagent ($Ti(O^iPr)_4$/(R,R)-diethyltartrate/H_2O/t-butyl hydroperoxide in a 1:2:1:1 molar ratio) oxidized prochiral sulfides to optically active sulfoxides. The observed enantiomeric excesses (ee) ranged between 75 and 90% for alkyl aryl sulfoxides and 50-71% for dialkyl sulfoxides.[180-183]

The use of chiral solvents in the metal-catalyzed asymmetric oxidation of sulfides with t-butyl hydroperoxide has been investigated using the metal catalysts, $Mo(O)_2(acac)_2$ and $V(O))acac)_2$, at temperatures between -10 and 25°C.[184] The large asymmetric induction observed suggests the entering of one or more of the chiral solvent molecules into the metal coordination sphere.

In the presence of a catalytic amount of optically active Schiff base oxovanadium(IV) complexes, Fujita and co-workers reported the asymmetric oxidation of sulfides to their corresponding chiral sulfoxides using t-butyl hydroperoxide.[185,186] In most cases, enantiomeric excesses between 20 and 40% were obtained.

In this work, the transition metal-catalyzed oxidation of n-butyl sulfide to the corresponding sulfoxide and sulfone in the solvent, 1-methyl-2-pyrrolidinone, by either the activation of molecular oxygen under mild conditions, or the activation of hydroperoxides under ambient conditions is presented. The characteristics of these reactions are described in terms of a recently developed classification scheme for transition metal-catalyzed organic substrate oxidations.[26,27]

Results and Discussion

Activation of Molecular Oxygen

One of the oxidative systems investigated involved the activation of molecular oxygen in the solvent, 1-methyl-2-pyrrolidinone, under mild conditions. In this system, we have reported the use of 1-methyl-2-pyrrolidinone in a catalytic cycle employing molecular hydrogen and oxygen in the presence of transition metal catalysts to provide a regenerative in situ hydroperoxide system for organic substrate oxidations (Figure 2-5).[24,25]

When reacted with molecular oxygen at 75°C, 1-methyl-2-pyrrolidinone is converted to the corresponding hydroperoxide, 5-hydroperoxo-1-methyl-2-pyrrolidinone. Early work showed N-methylsuccinimide to be the final hydroperoxide decomposition product (Figure 2-5, path (a)).[17] As a result, the exact mechanistic route for the decomposition of 5-hydroperoxo-1-methyl-2-pyrrolidinone in this system was pursued.[24,25] In a

$^{13}C/^{31}P$ NMR study of the oxidation of PPh_3, 5-hydroperoxo-1-methyl-2-pyrrolidinone was found to quantitatively oxidize PPh_3 to $OPPh_3$ by oxygen atom transfer to give the amido-alcohol intermediate, 5-hydroxy-1-methyl-2-pyrrolidinone (Figure 2-5, path (b)).[24,25] Using either homogeneous or heterogeneous catalysts, N-methylsuccinimide was reduced with H_2 at 100°C to the hydroperoxide precursor, 1-methyl-2-pyrrolidinone.[24,25]

In the absence or presence of transition metal catalysts, this in situ generated hydroperoxide system showed a high selectivity to the formation of sulfoxide in the oxidation of n-butyl sulfide (Table 4-1). The simple metal salts, $CoCl_2 \cdot 6H_2O$, $FeCl_3 \cdot 6H_2O$, and $FeSO_4 \cdot 7H_2O$ led to complete oxidation of the substrate in 6 hours. The short completion times observed for these reactions can be explained by the ability of these complexes to catalyze the formation of alkyl hydroperoxides through radical-chain mechanisms (Class IV behavior),[26,27] followed by the oxidation of the substrate via the metal-catalyzed decomposition of the N-alkylamide hydroperoxide (Haber-Weiss or Fenton chemistry).

Although requiring a longer reaction time, the μ_3-oxo trinuclear carboxylate complex, $[Fe_3O(OAc)_3(H_2O)_6]$ (where OAc=acetate), showed very good selectivity to sulfoxide formation via Class IVa[26,27] behavior (Table 4-1).

The complete oxidation of the thioether to the corresponding sulfoxide and sulfone was observed with the catalysts, $RuCl_3 \cdot 3H_2O$ and $[Ru_3O(pfb)_6(Et_2O)](pfb)$ (where

Table 4-1 Transition Metal-Catalyzed Oxidations of n-Butyl Sulfide Using 5-Hydroperoxo-1-methyl-2-pyrrolidinone (in situ).

Catalyst	Time (hours)	Products (%)
none	96	R_2SO (83) R_2SO_2 (17)
$CoCl_2 \cdot 6H_2O$	6	R_2SO (98) R_2SO_2 (2)
$FeCl_3 \cdot 6H_2O$	6	R_2SO (97) R_2SO_2 (3)
$FeSO_4 \cdot 7H_2O$	6	R_2SO (100) R_2SO_2 (0)
$[Fe_3O(OAc)_3(H_2O)_6]$	68	R_2SO (99) R_2SO_2 (1)
$RuCl_3 \cdot 3H_2O$	24	R_2SO (76) R_2SO_2 (24)
$[Ru_3O(pfb)_6(Et_2O)_3](pfb)$	24	R_2SO (84) R_2SO_2 (16)
Mn(TPP)Cl	132	R_2SO (53)[a] R_2SO_2 (0)
$Mo(O)_2(acac)_2$	72	R_2SO (80) R_2SO_2 (20)
$V(O)(acac)_2$	24	R_2SO (65) R_2SO_2 (35)

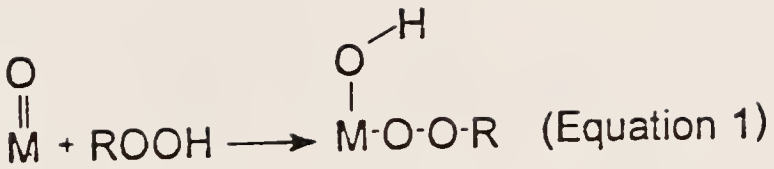
Note: Reaction conditions:
substrate (2.9×10^{-2} moles)
catalyst (2.9×10^{-5} moles)
NMP (4.7×10^{-1} moles)
run under O_2 (50 psig) at 75°C.

a. Unreacted substrate (47%) still remaining.

pfb=perfluorobutyrate) in 24 hours of reaction in the in situ generated 5-hydroperoxo-1-methyl-2-pyrrolidinone system (Table 4-1). As a result of the large O_2 uptake seen in these catalytic systems, these catalysts appear to exhibit Class IV[26,27] behavior both in the formation of 5-hydroperoxo-1-methyl-2-pyrrolidinone and the subsequent oxidation of the substrate.

Even though a 100% selectivity to sulfoxide was observed with the catalyst, Mn(TPP)Cl (where TPP=tetraphenylporphyrin), a lower conversion was observed as a result of the catalyst's hydroperoxide decomposition ability, which results from a "Fenton-like" homolytic cleavage of the alkyl hydroperoxide oxygen-oxygen bond (Table 4-1).[116] Furthermore, a gradual destruction of the catalyst, resulting from the oxidation of the porphyrin ligand, was observed. The large amount of O_2 uptake and non-productive utilization of the alkyl hydroperoxide are indicative of a sizeable Class IVa[26,27] component with this catalyst.

In order to obtain a more efficient use of the in situ generated N-alkylamide hydroperoxide, high-valent early transition metal complexes were investigated. Many of these systems operate by the addition of the hydroperoxide to a metal oxo functionality (Figure 4-3, Equation (1)), or by the displacement of a metal alkoxy group by hydroperoxide to yield a coordinated peroxide (Class IVb)[26,27] (Figure 4-3, Equation (2)). Utilizing alkyl hydroperoxides as the oxidant, the $Mo(O)_2(acac)_2$- and $V(O)(acac)_2$-catalyzed oxidations have been



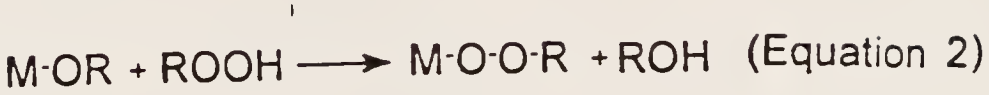


Figure 4-3 Formation of Metal Alkylperoxo Species.

proposed to proceed by way of a metal-alkylperoxo species.[172,173,175] In an extensive study by Modena and co-workers using t-butyl hydroperoxide, evidence was presented for the solvolysis of the acetylacetonate complex, $V(O)(acac)_2$, to a vanadate ester, $V(O)(OR)_3$.[173] This compound then reacts with the alkyl hydroperoxide to produce the active species, $V(O)(OR_3)(OOR)$. Attack of the sulfide on this metal alkylperoxo species results in the formation of sulfoxide and one equivalent of alcohol. Most other high-valent metal oxo complexes are proposed to proceed through similar pathways. As with the epoxidation of olefins by these complexes, pathways which do (and do not) involve pre-coordination of the substrate to the metal are proposed (Figure 4-4).[69,71]

$Mo(O)_2(acac)_2$, with its heterolytic pathway, showed a complete conversion of the thioether to the corresponding sulfoxide and sulfone in 72 hours using the in situ generated 5-hydroperoxo-1-methyl-2-pyrrolidinone (Table 4-1). This longer reaction time results from the inability of the complex to catalyze the free-radical formation of the N-alkylamide hydroperoxide. As a result of the Class IVb[26,27] behavior of this catalyst, a lesser amount of O_2 uptake was observed.

Another metal oxo complex, $V(O)(acac)_2$, completely oxidized the substrate in a reaction time of 24 hours (Table 4-1). This shorter reaction time and the large amount of O_2 uptake observed for this Class IVb[26,27] catalyst seems to suggest the involvement of a considerable Class IVa[26,27]

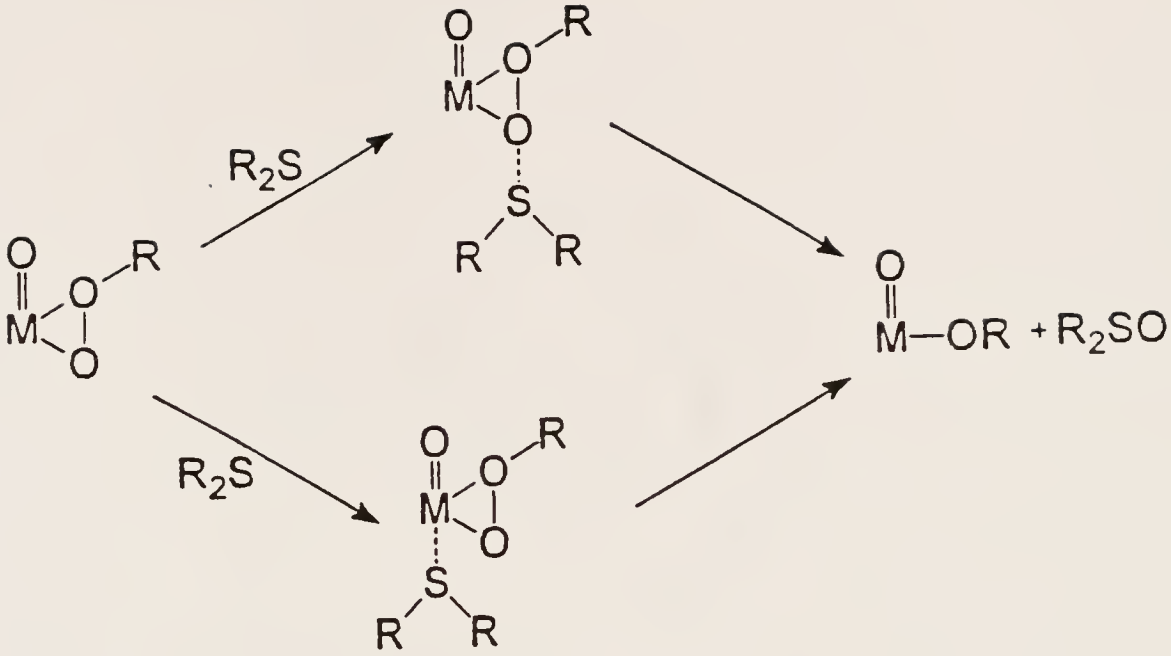


Figure 4-4 Sulfide Oxidations by Side-On Bonded Metal Peroxo Complexes.

component, which greatly facilitates the formation of the N-alkylamide hydroperoxide via a metal-catalyzed free-radical pathway.

From the results presented, the utilization of a transition metal complex possessing both Class IVa[26,27] and/or Class IVb[26,27] components is desirable. The reaction to form the alkyl hydroperoxide is catalyzed by metal complexes through radical-chain mechanisms, which belong to Class IVa.[26,27] Initiation occurs by an outer electron transfer to produce the radical cation, which then loses a proton to the base, solvent, or substrate to form the corresponding alkyl-radical (Figure 4-5). The subsequent reaction of the alkyl-radical with molecular oxygen produces the alkylperoxy-radical which undergoes further reaction with another substrate molecule to form the alkyl hydroperoxide and another alkyl-radical. The reduced metal species is reoxidized by molecular oxygen. Even though the reaction completion times are shorter, transition metal catalysts possessing a large Class IVa[26,27] component lead to less efficient use of the in situ generated N-alkylamide hydroperoxide as the result of the subsequent metal-catalyzed decomposition of the alkyl hydroperoxide.

The use of metal oxo (Class III)[26,27] or metal alkylperoxo (Class IVb)[26,27] complexes, or metal complexes possessing large Class III or IVb[26,27] components would result in a more efficient use of the alkyl hydroperoxide in the oxidation of organic substrates. With these facts in mind, the most

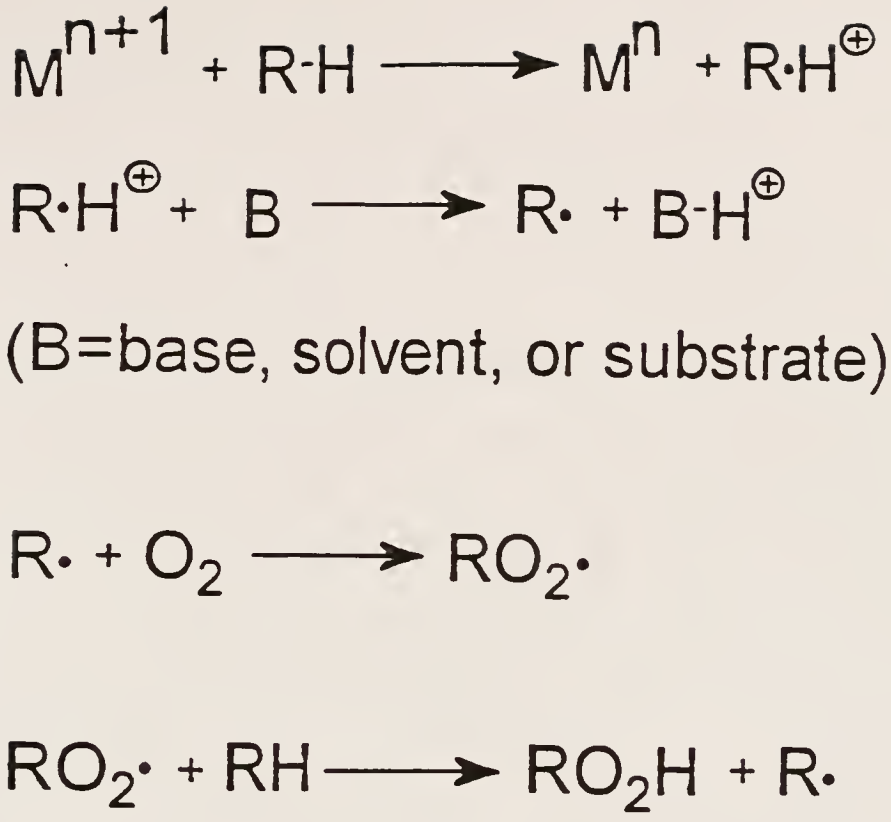

$M^{n+1} + R\text{-}H \longrightarrow M^{n} + R{\cdot}H^{\oplus}$
$R{\cdot}H^{\oplus} + B \longrightarrow R{\cdot} + B\text{-}H^{\oplus}$
(B=base, solvent, or substrate)
$R{\cdot} + O_2 \longrightarrow RO_2{\cdot}$
$RO_2{\cdot} + RH \longrightarrow RO_2H + R{\cdot}$

Figure 4-5 Catalytic Hydroperoxide Formation Via Class IVa Metal Catalysts.[26,27]

desirable metal complex for use in an in situ generated hydroperoxide system for the oxidation of organic substrates should possess a Class IVa[26,27] component for the catalytic formation of the alkyl hydroperoxide and a larger Class III (or Class IVb)[26,27] component for efficient use of the alkyl hydroperoxide in the subsequent substrate oxidation.

Activation of Alkyl Hydroperoxides

Several oxidative systems investigated involved the activation of alkyl hydroperoxides by transition metal complexes in the solvent, 1-methyl-2-pyrrolidinone, under ambient conditions. The alkyl hydroperoxides, 5-hydroperoxo-1-methyl-2-pyrrolidinone (pre-generated) and t-butyl hydroperoxide, employed in these reactions allowed us to determine the role of the transition metal complexes in the catalytic systems using 5-hydroperoxo-1-methyl-2-pyrrolidinone (in situ and pre-generated) as the oxidant. The results obtained with 5-hydroperoxo-1-methyl-2-pyrrolidinone (pre-generated) were compared with the results obtained in the analogous reactions using the well-known alkyl hydroperoxide, t-butyl hydroperoxide.

Using a 3:1 oxidant to substrate molar ratio, low conversions of the sulfide to the corresponding sulfoxide and/or sulfone were observed with the metal catalysts, $CoCl_2 \cdot 6H_2O$, $FeCl_3 \cdot 6H_2O$, and $RuCl_3 \cdot 3H_2O$ (Tables 4-2 and 4-3). The low yields of oxidized products seen with these catalysts are indicative of the metal-catalyzed decomposition of the

Table 4-2 Transition Metal-Catalyzed Oxidation of n-Butyl Sulfide Using 5-Hydroperoxo-1-methyl-2-pyrrolidinone.

Catalyst	Time (min.)	Products (%)
none	5	R_2SO (3)
	30	R_2SO (4)
	60	R_2SO (4)
$CoCl_2 \cdot 6H_2O$	5	R_2SO (20) R_2SO_2 (2)
	30	R_2SO (24) R_2SO_2 (3)
	60	R_2SO (24) R_2SO_2 (3)
$FeCl_3 \cdot 6H_2O$	5	R_2SO (10)
	30	R_2SO (10)
	60	R_2SO (10)
$RuCl_3 \cdot 3H_2O$	5	R_2SO (38) R_2SO_2 (2)
	30	R_2SO (38) R_2SO_2 (2)
	60	R_2SO (38) R_2SO_2 (2)

Table 4-2--Continued.

Catalyst	Time (min.)	Products (%)
$Mo(O)_2(acac)_2$	5	R_2SO (57) R_2SO_2 (12)
	30	R_2SO (66) R_2SO_2 (28)
	60	R_2SO (60) R_2SO_2 (36)
	360	R_2SO (35) R_2SO_2 (65)
	1440	R_2SO (13) R_2SO_2 (87)
	2880	R_2SO_2 (100)
$V(O)(acac)_2$	5	R_2SO (77) R_2SO_2 (18)
	30	R_2SO (64) R_2SO_2 (36)
	60	R_2SO (64) R_2SO_2 (36)

Note: Reaction conditions:
substrate ($1.6x10^{-3}$ moles)
catalyst ($1.6x10^{-4}$ moles)
NMP (10 mL)
NMP-OOH ($4.9x10^{-3}$ moles)
run under N_2 at ambient conditions.

Table 4-3 Transition Metal-Catalyzed Oxidation of n-Butyl Sulfide Using t-Butyl Hydroperoxide.

Catalyst	Time (min.)	Products (%)
none	5	R_2SO (4)
	30	R_2SO (4)
	60	R_2SO (4)
$CoCl_2 \cdot 6H_2O$	5	R_2SO (23)
	30	R_2SO (23)
	60	R_2SO (23)
$FeCl_3 \cdot 6H_2O$	5	R_2SO (9)
	30	R_2SO (9)
	60	R_2SO (9)
$RuCl_3 \cdot 3H_2O$	5	R_2SO (38)
	30	R_2SO (38)
	60	R_2SO (38)
$Mo(O)_2(acac)_2$	5	R_2SO (56)
	30	R_2SO (65) R_2SO_2 (4)
	60	R_2SO (75) R_2SO_2 (6)
	360	R_2SO (83) R_2SO_2 (17)
	1440	R_2SO (25) R_2SO_2 (75)
	2880	R_2SO_2 (100)

Table 4-3--Continued.

Catalyst	Time (min.)	Products (%)
$V(O)(acac)_2$	5	R_2SO (38) R_2SO_2 (2)
	30	R_2SO (47) R_2SO_2 (4)
	60	R_2SO (55) R_2SO_2 (5)
	360	R_2SO (81) R_2SO_2 (19)
	1440	R_2SO (81) R_2SO_2 (19)

Note: Reaction conditions:
substrate (1.6×10^{-3} moles)
catalyst (1.6×10^{-4} moles)
NMP (10 mL)
t-BuOOH (4.9×10^{-3} moles)
run under N_2 at ambient conditions.

alkyl hydroperoxide via a radical process (Class IVa),[26,27] leading to the inefficient utilization of the oxidant in the oxidation of the sulfide.

Looking at the metal oxo complexes, $Mo(O)_2(acac)_2$ and $V(O)(acac)_2$, high conversions of the substrate to the corresponding sulfoxide and sulfone were seen with the use of a 3:1 oxidant to sulfide molar ratio (Tables 4-2 and 4-3). In both the 5-hydroperoxo-1-methyl-2-pyrrolidinone and t-butyl hydroperoxide reactions, the $Mo(O)_2(acac)_2$ catalyst completely oxidized the sulfide to the corresponding sulfone, while the catalyst, $V(O)(acac)_2$, gave predominantly the sulfoxide. The results presented in Tables 4-2 and 4-3 for these metal catalysts would seem to suggest the involvement of Class IVb[26,27] behavior for both the $Mo(O)_2(acac)_2$ and the $V(O)(acac)_2$ catalysts with a presence of a substantial Class IVa[26,27] component with $V(O)(acac)_2$.

To test this suggested difference in $Mo(O)_2(acac)_2$ and $V(O)(acac)_2$, a series of experiments were performed using the catalysts, $Mo(O)_2(acac)_2$ or $V(O)(acac)_2$, in 1-methyl-2-pyrrolidinone solvent using a 1:1 oxidant to substrate ratio (Table 4-4). The metal catalyst, $Mo(O)_2(acac)_2$ exhibits very efficient use of the alkyl hydroperoxides (96% for 5-hydroperoxo-1-methyl-2-pyrrolidinone and 94% for t-butyl hydroperoxide). Hence, this metal catalyst functions in a Class IVb manner.[26,27] On the other hand, the analogous sulfide oxidations using $V(O)(acac)_2$ in 1-methyl-2-pyrrolidinone showed much lower efficiencies in the use of the

Table 4-4 Efficiency of Alkyl Hydroperoxide Utilization.

Catalyst	Oxidant	Time (min.)	Products (%)
$Mo(O)_2(acac)_2$	NMP-OOH (pre-gen)	5	R_2SO (42) R_2SO_2 (6)
		30	R_2SO (60) R_2SO_2 (18)
		60	R_2SO (60) R_2SO_2 (18)
$Mo(O)_2(acac)_2$	t-BuOOH	5	R_2SO (40) R_2SO_2 (2)
		30	R_2SO (64) R_2SO_2 (15)
		60	R_2SO (64) R_2SO_2 (15)
$V(O)(acac)_2$	NMP-OOH (pre-gen)	5	R_2SO (20)
		30	R_2SO (51)
		60	R_2SO (51)
$V(O)(acac)_2$	t-BuOOH	5	R_2SO (16)
		30	R_2SO (50)
		60	R_2SO (50)

Note: Reaction conditions:
substrate (1.6×10^{-3} moles)
catalyst (1.6×10^{-4} moles)
NMP (10 mL)
oxidant (1.6×10^{-3} moles)
run under N_2 at ambient conditions.

alkyl hydroperoxides in the substrate oxidations (51% for 5-hydroperoxo-1-methyl-2-pyrrolidinone and 50% for t-butyl hydroperoxide). These results show that $V(O)(acac)_2$ exhibits Class IVb behavior with a substantial Class IVa[26,27] component, which leads to non-productive hydroperoxide decomposition.

As a result of an earlier solvent variation study involving the $Mo(O)_2(acac)_2$-catalyzed oxidation of trans-β-methylstyrene using alkyl hydroperoxides, the involvement of a linear alkylperoxo metal complex as the active species in the coordinating, polar solvent, 1-methyl-2-pyrrolidinone, was suggested. The involvement of this Class IVb[26,27] behavior has been proposed in the $Mo(O)_2(acac)_2$ and $V(O)(acac)_2$-catalyzed sulfide oxidations using alkyl hydroperoxides as the oxidant. In the solvent 1-methyl-2-pyrrolidinone, the oxidation of n-butyl sulfide in the presence of $Mo(O)_2(acac)_2$ or $V(O)(acac)_2$ probably involves a linear metal alkylperoxo species (Class IVb).[26,27]

Another interesting aspect of the $V(O)(acac)_2$-catalyzed sulfide oxidations in 1-methyl-2-pyrrolidinone using either 5-hydroperoxo-1-methyl-2-pyrrolidinone or t-butyl hydroperoxide is the recyclability of the catalyst. When a solution of n-butyl sulfide and $V(O)(acac)_2$ was reacted with the alkyl hydroperoxide in a 1:1 oxidant to sulfide molar ratio, the green solution underwent an instantaneous red-orange color change. After a 24 hour reaction time, the resulting green solution showed a 51% efficient use of the alkyl hydroperoxide, 5-hydroperoxo-1-methyl-2-pyrrolidinone in the

oxidation of the substrate (Table 4-5). Subsequent additions of 5-hydroperoxo-1-methyl-2-pyrrolidinone at 24 hour intervals showed efficiencies of 5-hydroperoxo-1-methyl-2-pyrrolidinone use of 42-43% and the green to red-orange to green color changes taking place. Analogous behavior was observed for the t-butyl hydroperoxide reaction with efficiencies of alkyl peroxide use of 40-50% (Table 4-5). The observed red-orange color is presumably due to the presence of a linear metal alkylperoxo species in the solvent 1-methyl-2-pyrrolidinone (Class IVb).[26,27]

The alkyl hydroperoxides, 5-hydroperoxo-1-methyl-2-pyrrolidinone and t-butyl hydroperoxide, show comparable reactivity in the solvent, 1-methyl-2-pyrrolidinone, in the presence of transition metal catalysts other than $V(O)(acac)_2$.

Activation of H_2O_2

Using 1-methyl-2-pyrrolidinone as the solvent, another oxidative system involving the activation of H_2O_2 by transition metal complexes was investigated under ambient conditions. Several desirable properties, such as miscibility with both H_2O and various organic solvents and the solubility of a large number of inorganic and organic compounds, make 1-methyl-2-pyrrolidinone a very good solvent for these reactions by allowing one to use a much safer 30% aqueous H_2O_2 solution without phase transfer methods. In addition to determining the role of the transition metal complexes in this catalytic system, the results obtained were

Table 4-5 Catalyst Recyclability.

Catalyst	Oxidant	Time (min.)	Products (%)
$V(O)(acac)_2$	NMP-OOH (pre-gen)	5	R_2SO (20)
		30	R_2SO (51)
		60	R_2SO (51)
		1440[a]	R_2SO (51)
		1445	R_2SO (65) R_2SO_2 (2)
		1470	R_2SO (74) R_2SO_2 (10)
		1550	R_2SO (74) R_2SO_2 (10)
		2880[a]	R_2SO (74) R_2SO_2 (10)
		2885	R_2SO (77) R_2SO_2 (15)
		2910	R_2SO (77) R_2SO_2 (23)
		2940	R_2SO (77) R_2SO_2 (23)

Table 4-5--Continued.

Catalyst	Oxidant	Time (min.)	Products (%)
$V(O)(acac)_2$	t-BuOOH	5	R_2SO (16)
		30	R_2SO (50)
		60	R_2SO (50)
		1440[a]	R_2SO (50)
		1445	R_2SO (64) R_2SO_2 (3)
		1470	R_2SO (73) R_2SO_2 (9)
		1550	R_2SO (73) R_2SO_2 (9)
		2880[a]	R_2SO (73) R_2SO_2 (9)
		2885	R_2SO (76) R_2SO_2 (14)
		2910	R_2SO (80) R_2SO_2 (20)
		2940	R_2SO (80) R_2SO_2 (20)

Note: Reaction conditions:
substrate (1.6×10^{-3} moles)
catalyst (1.6×10^{-4} moles)
NMP (10 mL)
oxidant (1.6×10^{-3} moles)
run under N_2 at ambient conditions.

a. Oxidant (1.6×10^{-3} moles) was added at these 24 hour intervals.

compared with the results obtained in the analogous reactions using the alkyl hydroperoxides, 5-hydroperoxo-1-methyl-2-pyrrolidinone (pre-generated) and t-butyl hydroperoxide.

The oxidation of n-butyl sulfide was investigated in neat 1-methyl-2-pyrrolidinone using a 3:1 oxidant to substrate molar ratio in the presence of several transition metal catalysts (Table 4-6). While the uncatalyzed reaction showed little oxidation taking place, the use of $CoCl_2 \cdot 6H_2O$ led to a sulfoxide conversion of 37%. In an analogous experiment employing a 1:1 oxidant to substrate molar ratio, a low efficiency in H_2O_2 utilization was observed with this catalyst (Table 4-7); thus, clearly demonstrating the predominance of the metal-catalyzed decomposition of H_2O_2 by a homolytic process (Class IVa).[26,27] Even though the catalyst, $FeCl_3 \cdot 6H_2O$, showed the complete oxidation of the substrate using a 3:1 oxidant to substrate molar ratio (Table 4-6), only a 57% efficient use of the oxidant was obtained (Table 4-7). The H_2O_2 efficiency seen with this complex suggests that the metal-catalyzed decomposition of the peroxide (Class IVa)[26,27] is a major contributing factor. Another promising catalyst in the 3:1 oxidant to substrate system, $RuCl_3 \cdot 3H_2O$, exhibited analogous behavior as well in the solvent, 1-methyl-2-pyrrolidinone (Tables 4-6 and 4-7). These three metal complexes exhibited analogous Class IVa[26,27] behavior in 1-methyl-2-pyrrolidinone, using alkyl hydroperoxide (Tables 4-2 and 4-3).

Table 4-6 n-Butyl Sulfide Oxidations Using H_2O_2.

Catalyst	Time (min.)	Products (%)
none[a]	5	none
	30	none
	60	none
none[b]	5	R_2SO (5)
	30	R_2SO (7)
	60	R_2SO (7)
$CoCl_2 \cdot 6H_2O$[a]	5	R_2SO (4)
	30	R_2SO (5)
	60	R_2SO (5)
$CoCl_2 \cdot 6H_2O$[b]	5	R_2SO (37)
	30	R_2SO (37)
	60	R_2SO (37)
$FeCl_3 \cdot 6H_2O$[a]	5	R_2SO (4)
	30	R_2SO (11)
	60	R_2SO (11)
$FeCl_3 \cdot 6H_2O$[b]	5	R_2SO (53) R_2SO_2 (46)
	30	R_2SO (47) R_2SO_2 (53)
	60	R_2SO (47) R_2SO_2 (53)

Table 4-6--Continued.

Catalyst	Time (min.)	Products (%)
$RuCl_3 \cdot 3H_2O$[a]	5	R_2SO (22) R_2SO_2 (5)
	30	R_2SO (22) R_2SO_2 (5)
	60	R_2SO (22) R_2SO_2 (5)
$RuCl_3 \cdot 3H_2O$[b]	5	R_2SO (75) R_2SO_2 (20)
	30	R_2SO (75) R_2SO_2 (20)
	60	R_2SO (75) R_2SO_2 (20)
$Mo(O)_2(acac)_2$[a]	5	R_2SO (9)
	30	R_2SO (25)
	60	R_2SO (35)
$Mo(O)_2(acac)_2$[b]	5	R_2SO (68) R_2SO_2 (31)
	30	R_2SO (58) R_2SO_2 (41)
	60	R_2SO (46) R_2SO_2 (54)
	360	R_2SO (25) R_2SO_2 (75)
	1440	R_2SO (3) R_2SO_2 (97)
	2880	R_2SO_2 (100)

Table 4-6--Continued.

Catalyst	Time (min.)	Products (%)
$V(O)(acac)_2$[a]	5	none
	30	none
	60	none
$V(O)(acac)_2$[b]	5	R_2SO (15) R_2SO_2 (81)
	30	R_2SO_2 (100)

a. Reaction conditions:

substrate (1.6×10^{-3} moles)
catalyst (1.6×10^{-4} moles)
H_2O_2 (4.9×10^{-3} moles, 30% aqueous solution)
NMP (5.0 mL)
H_2O (5.0 mL)
run under N_2 at ambient conditions.

b. Reaction conditions:

substrate (1.6×10^{-3} moles)
catalyst (1.6×10^{-4} moles)
H_2O_2 (4.9×10^{-3} moles, 30% aqueous solution)
NMP (10 mL)
run under N_2 at ambient conditions.

Table 4-7 Efficiency of H_2O_2 Utilization.

Catalyst	Time	Products (%)
$CoCl_2 \cdot 6H_2O$	5	R_2SO (8)
	30	R_2SO (8)
	60	R_2SO (8)
$FeCl_3 \cdot 6H_2O$	5	R_2SO (37)
	30	R_2SO (48)
	60	R_2SO (55) R_2SO_2 (2)
	90	R_2SO (55) R_2SO_2 (2)
$RuCl_3 \cdot 3H_2O$	5	R_2SO (36)
	30	R_2SO (45)
	60	R_2SO (45)
$Mo(O)_2(acac)_2$	5	R_2SO (64) R_2SO_2 (6)
	30	R_2SO (88) R_2SO_2 (6)
	60	R_2SO (88) R_2SO_2 (6)
$V(O)(acac)_2$	5	R_2SO (67)
	30	R_2SO (67)
	60	R_2SO (67)

Note: Reaction conditions:
substrate (1.6×10^{-3} moles)
catalyst (1.6×10^{-4} moles)
H_2O_2 (1.6×10^{-3} moles, 30% aqueous solution)
NMP (10 mL)
run under N_2 at ambient conditions.

As a result, metal complexes were sought that bound H_2O_2 (Class IVb)[26,27] in order to obtain a more efficient use of the oxidant. Using a 3:1 oxidant to substrate molar ratio, the near complete oxidation of the sulfide to sulfoxide (68%) and sulfone (31%) was observed in 5 minutes using $Mo(O)_2(acac)_2$ as the catalyst (Table 4-6). The efficiency of H_2O_2 use for this catalyst in an analogous reaction using a 1:1 oxidant to substrate molar ratio was 100% (Table 4-7); thereby, indicating Class IVb[26,27] behavior.

Using a 3:1 oxidant to substrate molar ratio, the complete oxidation of the sulfide to the corresponding sulfone was observed in 5 minutes with $V(O)(acac)_2$ (Table 4-6). This catalyst exhibited an efficiency for H_2O_2 utilization of 67% in an analogous 1:1 oxidant to substrate reaction (Table 4-7). This metal oxo complex would appear to possess a peroxide decomposition component (Class IVa).[26,27] Another interesting aspect about this system is the catalyst recyclability. Using 1-methyl-2-pyrrolidinone as the solvent, a solution of n-butyl sulfide and $V(O)(acac)_2$ was reacted with H_2O_2 at 24 hour intervals showing efficiencies of H_2O_2 use of 50-70% (Class IVb with a Class IVa component)[26,27] (Table 4-8). Analogous behavior was observed in the $V(O)(acac)_2$-catalyzed thioether oxidations using 5-hydroperoxo-1-methyl-2-pyrrolidinone (pre-generated) or t-butyl hydroperoxide (Table 4-5).

Looking at the results given in Table 4-6, the employment of neat 1-methyl-2-pyrrolidinone as a solvent led to a larger percentage of substrate oxidation than observed in the

Table 4-8 Catalyst Recyclability.

Catalyst	Time (min.)	Products (%)
$V(O)(acac)_2$	0	none
	5	R_2SO (67)
	30	R_2SO (67)
	60	R_2SO (67)
	1440[a]	R_2SO (67)
	1445	R_2SO (67) R_2SO_2 (33)
	1470	R_2SO (67) R_2SO_2 (33)
	1550	R_2SO (67) R_2SO_2 (33)
	2880[a]	R_2SO (67) R_2SO_2 (33)
	2885	R_2SO (16) R_2SO_2 (84)
	2910	R_2SO (16) R_2SO_2 (84)
	2940	R_2SO (16) R_2SO_2 (84)

Note: Reaction conditions:
substrate ($1.6x10^{-3}$ moles)
catalyst ($1.6x10^{-4}$ moles)
H_2O_2 ($1.6x10^{-3}$ moles, 30% aqueous solution)
NMP (10 mL)
run under N_2 at ambient conditions.

a. H_2O_2 ($1.6x10^{-3}$ moles, 30% aqueous solution) was added at the 24 hours intervals.

analogous reactions run in a 1-methyl-2-pyrrolidinone/H_2O (50/50, V/V) solvent system. The differences observed in the oxidative abilities of both of these solvent systems can be attributed to solvent effects on the oxidation and reduction potentials of the metal complexes and/or the oxidant, H_2O_2, and/or solubility factors.

In a series of experiments employing various 1-methyl-2-pyrrolidinone/H_2O ratios (V/V), the oxidation of n-butyl sulfide with the $Mo(O)_2(acac)_2$-catalyzed system exhibited a decrease with increasing amounts of H_2O (Table 4-9). A subsequent stability study of H_2O_2 in 1-methyl-2-pyrrolidinone (Table 4-10), 1-methyl-2-pyrrolidinone/H_2O (50/50, V/V) (Table 4-11), and H_2O (Table 4-12) under ambient conditions for 168 hours showed a decrease in the stability of H_2O_2 with increasing amounts of H_2O. The increased stability of the oxidant in the solvent, 1-methyl-2-pyrrolidinone, could be due to intermolecular interactions between the oxidant and the solvent.

Even though greater reactivity was observed in the H_2O_2 thioether oxidations, the role of the transition metal catalysts for H_2O_2 and the alkyl hydroperoxides, 5-hydroperoxo-1-methyl-2-pyrrolidinone (pre-generated) and t-butyl hydroperoxide, are comparable in the solvent, 1-methyl-2-pyrrolidinone.

Table 4-9 1-Methyl-2-pyrrolidinone/H_2O Ratio Variations.

Time (min.)	Products (%)	NMP/H_2O Ratio (%V/%V)					
		(100/0)	(90/10)	(80/20)	(70/30)	(60/40)	(50/50)
5	R_2SO R_2SO_2	68 31	60 22	53 10	22 1	15 0	9 0
30	R_2SO R_2SO_2	58 41	56 37	51 12	47 3	41 1	35 0
60	R_2SO R_2SO_2	46 54	40 54	56 20	51 4	45 2	40 1
360	R_2SO R_2SO_2	25 75	35 60	60 24	55 8	47 2	45 2
720	R_2SO R_2SO_2	15 85	21 74	40 44	57 9	48 4	45 2
1440	R_2SO R_2SO_2	3 97	3 92	40 45	57 11	49 6	45 2
2880	R_2SO R_2SO_2	0 100	0 100	40 45	57 11	49 6	45 2

Note: Reaction conditions:
substrate (1.6×10^{-3} moles)
$Mo(O)_2(acac)_2$ (1.6×10^{-4} moles)
H_2O_2 (4.9×10^{-3} moles, 30% aqueous solution)
$V_{solvent}$ (10 mL)
run under N_2 at ambient conditions.

Table 4-10 Stability of H_2O_2 in 1-Methyl-2-pyrrolidinone.

Time (hours)	[ROOH], M
0	0.49
24	0.49
96	0.48
168	0.47

Note: Reaction conditions:
H_2O_2 (4.9×10^{-3} moles, 30% aqueous solution)
NMP (10 mL)
run under ambient conditions.

Table 4-11 Stability of H_2O_2 in 1-Methyl-2-pyrrolidinone/H_2O (50/50).

Time (hours)	[ROOH], M
0	0.49
24	0.44
96	0.38
168	0.31

Note: Reaction conditions:
H_2O_2 (4.9×10^{-3} moles, 30% aqueous solution)
NMP (5.0 mL)
H_2O (5.0 mL)
run under ambient conditions.

Table 4-12 Stability of H_2O_2 in H_2O.

Time (hours)	[ROOH], M
0	0.49
24	0.42
96	0.34
168	0.29

Note: Reaction conditions:
H_2O_2 (4.9×10^{-3} moles, 30% aqueous solution)
H_2O (10 mL)
run under ambient conditions.

Experimental

Reagents and Equipment

The n-butyl sulfide, n-butyl sulfoxide, n-butyl sulfone, and 1-methyl-2-pyrrolidinone (HPLC Grade) were obtained from Aldrich Chemical Company and were used as received. The metal complexes, $Mo(O)_2(acac)_2$, $V(O)(acac)_2$, and $RuCl_3 \cdot 3H_2O$ were received from Aldrich Chemical Company as well. All other reagents and solvents were obtained from Fischer Scientific and used as received.

All sulfide oxidations using the in situ generated N-alkylamide hydroperoxide derived from 1-methyl-2-pyrrolidinone were run in a Parr Pressure Apparatus at the indicated temperature and pressure.

CAUTION! Extreme care should be taken when working with a pressurized apparatus at or above room temperature. Appropriate shields must be used and fire extinguishers should be nearby. For elevated temperatures, the reaction solution should be cooled to room temperature before disassembling the pressure apparatus.

The 5-hydroperoxo-1-methyl-2-pyrrolidinone (pre-generated) was prepared by a previously described method.[24,25]

The t-butyl hydroperoxide was used as a 90% by weight solution, containing t-butyl alcohol (5%) and H_2O (5%).

The H_2O_2 was used as a 30% by weight aqueous solution.

Peroxide concentrations were determined by iodometric titrations.[33]

CAUTION! Many hydroperoxides are shock/temperature sensitive and should be treated as potentially explosive.

A Varian 3700 GC with an FID and Hewlett Packard 3390A integrator was used to analyze the oxidation reactions, using a 6 foot stainless steel column packed with Carbowax 20M (10%) on Chromosorb WHP (80/100 mesh). The substrate(s) and product(s) were identified and quantified using known standards.

The complexes, $[Fe_3O(OAc)_3(H_2O)_6]$ and $[Ru_3O(pfb)_6(Et_2O)_3](pfb)$, were prepared by previously reported methods.[187,188]

Sulfide Oxidations Using 5-Hydroperoxo-1-methyl-2-pyrrolidinone (in situ)

1-Methyl-2-pyrrolidinone (45 mL), n-butyl sulfide (42g, $2.9x10^{-2}$ moles), and the appropriate catalyst ($2.9x10^{-5}$ moles, see Table 4-1) were placed in a 250 mL Parr Pressure Bottle equipped with magnetic stirring. After the pressure apparatus was assembled, the reactor was purged 3 times with O_2 (50 psig) and then pressurized with O_2 (50 psig). The reactor was placed in a 75°C oil bath. Recharging with O_2 (50 psig) was performed as needed. Samples were drawn periodically and analyzed by GC.

Sulfide Oxidations Using 5-Hydroperoxo-1-methyl-2-pyrrolidinone (pre-generated), t-Butyl Hydroperoxide, and H_2O_2

1-Methyl-2-pyrrolidinone (10 mL), n-butyl sulfide (0.23g,$1.6x10^{-3}$ moles), and the appropriate catalyst ($1.6x10^{-4}$

moles, see Tables 4-2, 4-3, and 4-6) were placed in a 100 mL round bottom flask equipped with magnetic stirring and an N_2 atmosphere. After 30 minutes of stirring, the appropriate oxidant ($4.9x10^{-3}$ moles, see Tables 4-2, 4-3, and 4-6) was added dropwise to the reaction solution. Samples were drawn periodically and analyzed by GC.

ROOH and H_2O_2 Efficiency Studies

1-Methyl-2-pyrrolidinone (10 mL), n-butyl sulfide (0.23g,$1.6x10^{-3}$ moles), and the appropriate catalyst ($1.6x10^{-4}$ moles, see Tables 4-4 and 4-7) were placed in a 100 mL round bottom flask equipped with magnetic stirring and an N_2 atmosphere. After 30 minutes of stirring, the appropriate alkyl hydroperoxide ($1.6x10^{-3}$ moles, see Tables 4-4 and 4-7) was added dropwise to the reaction solution. Samples were drawn periodically and analyzed by GC.

Catalyst Recyclability Using Alkyl Hydroperoxides and H_2O_2

1-Methyl-2-pyrrolidinone (10 mL), n-butyl sulfide (0.23g,$1.6x10^{-3}$ moles) and $V(O)(acac)_2$ (0.0424g, $1.6x10^{-4}$ moles) were placed in a 100 mL round bottom flask equipped with magnetic stirring and an N_2 atmosphere. After 30 minutes of stirring, a green solution resulted. At successive 24 hour intervals, the appropriate oxidant ($1.6x10^{-3}$ moles, see Tables 4-5 and 4-8) was added dropwise to the reaction solution, followed by periodic GC analyses.

Sulfide Oxidations in 1-Methyl-2-pyrrolidinone/H_2O (50/50, V/V)

1-Methyl-2-pyrrolidinone (5.0 mL), distilled H_2O (5.0 mL), n-butyl sulfide (0.23g, $1.6x10^{-3}$ moles), and the appropriate catalyst ($1.6x10^{-4}$ moles, see Table 4-6) were placed in a 100 mL round bottom flask equipped with magnetic stirring and an N_2 atmosphere. After 30 minutes of stirring, H_2O_2 ($4.9x10^{-3}$ moles) was added dropwise to the reaction solution. Samples were drawn periodically and analyzed by GC.

Effects of H_2O on Sulfide Oxidations

$Mo(O)_2(acac)_2$ (0.0522g, $1.6x10^{-4}$ moles), n-butyl sulfide (0.23g, $1.6x10^{-3}$ moles), and the appropriate 1-methyl-2-pyrrolidinone/H_2O ratio (10 mL total volume, see Table 4-9) were placed in a 100 mL round bottom flask equipped with magnetic stirring and N_2 atmosphere. After 30 minutes of stirring, H_2O_2 ($1.6x10^{-3}$ moles) was added dropwise to the reaction solution. Samples were drawn periodically and analyzed by GC.

Stability Studies of H_2O_2 in Various Solvent Systems

Solutions of H_2O_2 ($1.6x10^{-3}$ moles) in 1-methyl-2-pyrrolidinone (10 mL), 1-methyl-2-pyrrolidinone/H_2O (50/50, V/V, 10 mL total volume), and H_2O (10 mL) were prepared and compared by iodometric titrations over a period of 168 hours under ambient conditions.

Conclusions

Thioethers, such as n-butyl sulfide, can be oxidized to the corresponding sulfoxides and sulfones in the solvent, 1-methyl-2-pyrrolidinone, by either the activation of molecular oxygen under mild conditions, or the activation of hydroperoxides under ambient conditions.

When reacted with molecular oxygen at 75°C, 1-methyl-2-pyrrolidinone is converted to the corresponding alkyl hydroperoxide, 5-hydroperoxo-1-methyl-2-pyrrolidinone, which completely oxidizes the sulfide to the corresponding sulfoxide and sulfone in the presence of transition metal complexes. Both the completion times and the product selectivities are dependent on the nature of the transition metal catalyst used. Shorter reaction times and less efficient utilization of the alkyl hydroperoxide are observed with radical-chain catalysts (Class IVa).[26,27] More efficient use of the alkyl hydroperoxide and longer reaction times result with the use of metal oxo complexes that bind the hydroperoxide (Class IVb).[26,27] The longer reaction times seen result from the inability of the catalyst to initiate the formation of the N-alkylamide hydroperoxide via a peroxy-radical mechanism.

Under ambient conditions, the alkyl hydroperoxides, 5-hydroperoxo-1-methyl-2-pyrrolidinone and t-butyl hydroperoxide, show comparable reactivity in the solvent, 1-methyl-2-pyrrolidinone, in the presence of transition metal catalysts. The metal oxo complexes, $Mo(O)_2(acac)_2$ and $V(O)(acac)_2$, exhibited higher efficiencies for alkyl

hydroperoxide utilization; thereby, providing more complete oxidation of the substrate (Class IVb).[26,27] These metal-catalyzed alkyl hydroperoxide results aided in the determination of the exact role of the transition metal complexes in the in situ generated 5-hydroperoxo-1-methyl-2-pyrolidinone system.

Even though greater reactivity was observed in the metal-catalyzed thioether oxidations using H_2O_2 under ambient conditions, the role of the transition metal complexes is comparable to those for the alkyl hydroperoxides, 5-hydroperoxo-1-methyl-2-pyrrolidinone and t-butyl hydroperoxide. The increased activity of H_2O_2 may be due in part to the stabilizing effect of the intermolecular interactions between the oxidant and the solvent. This solvent aided stability, coupled with the use of the metal oxo complexes, $Mo(O)_2(acac)_2$ and $V(O)(acac)_2$, result in a very efficient use of the oxidant in the oxidation of the substrate in 1-methyl-2-pyrrolidinone (Class IVb).[26,27]

CHAPTER 5
PEROXYACID OXIDATIONS OF THIOETHERS IN 1-METHYL-2-PYRROLIDINONE SOLVENT

Introduction

It has long been known that organic peroxyacids are much stronger oxidants than H_2O_2 and are able to oxidize thioethers to their corresponding sulfoxides and sulfones under mild conditions.[147] Some of the organic peroxyacids used in the oxidation of thioethers include peroxyacetic acid, m-chloroperoxybenzoic, momoperoxyphthalic acid, peroxymaleic acid, and trifluoroperoxyacetic acid.[189-194]

Thioethers are converted to sulfoxides by a mechanism involving an intramolecular proton transfer (Figure 5-1).[195] Using less reactive organic peroxyacids, the further oxidation of sulfoxides to the corresponding sulfones occurs in a similar manner at a much slower rate.[196-198] On the other hand, the use of highly reactive organic peroxyacids, such as trifluoroperoxyacetic acid, in the oxidation of thioethers can lead directly to the corresponding sulfones.[199]

Overberger and Cummins studied the oxidation of p,p-dichlorobenzyl sulfide using a series of para-substituted peroxybenzoic acids.[200] These experiments showed an increased oxidation rate with electron-withdrawing groups and a

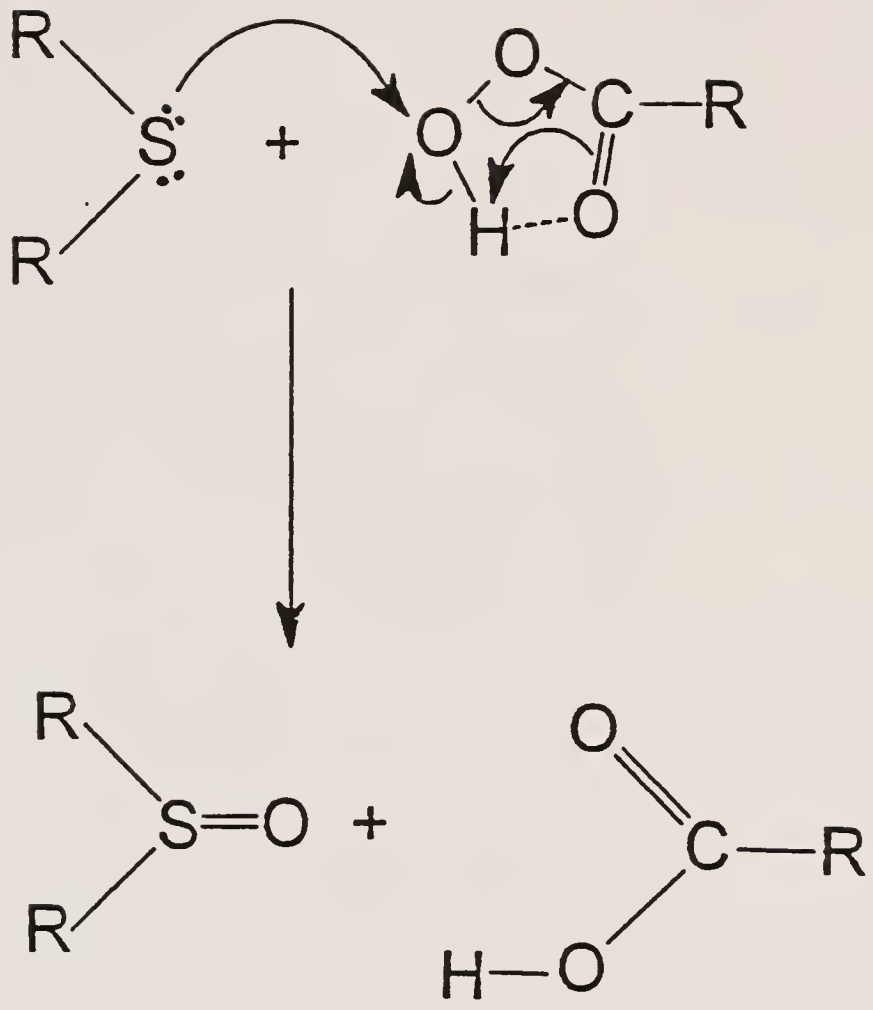


Figure 5-1 Thioether Oxidation Using Organic Peroxyacids.[195]

decreased oxidation rate with electron-donating groups. Similar results were obtained by Szmant et al. in the oxidation of diphenyl sulfide.[201]

In both acidic and alkaline media, Curci et al. reported that electron-withdrawing groups showed an increase in the rates of oxidation of p-tolyl methyl sulfoxide.[202]

Peroxymaleic acid was prepared by the reaction of maleic anhydride and 90% H_2O_2 in an inert solvent.[194] This organic peroxyacid exhibited a much greater oxidizing ability than other laboratory peroxyacids with the exception of trifluoroperoxyacetic acid. Using the in situ generated peroxymaleic acid, diallyl sulfoxide was oxidized to the corresponding sulfone in an 87% yield in methylene chloride at 0°C.

Harrison and Hodge investigated the oxidation of thioethers using a polymer-supported peroxyacid.[203] When reacted in a 1:1 oxidant to substrate ratio, tetrahydrothiophen and L-methionine yielded the corresponding sulfoxides and sulfones. Higher yields of the corresponding sulfones were obtained using a 2:1 oxidant to substrate ratio.

The use of transition metal complexes in the oxidation of thioethers by organic peroxyacids has received little attention. Doumaux et al. oxidized thioethers to the corresponding sulfones in the presence of a catalytic amount of $Mn(acac)_3$ using H_2O_2 in acetic acid.[9] The reactive oxidant was suggested to be peroxyacetic acid.

In the presence of a catalytic amount of the catalyst, $[Fe(CH_3CN)_4][ClO_4]_2$, m-chloroperoxybenzoic acid oxidized

diphenyl sulfide and diphenyl sulfoxide to the corresponding sulfoxide and sulfone, respectively.[171] The oxidation of these sulfur-containing substrates exhibited 51-71% efficiencies in peroxyacid utilization.

The asymmetric oxidation of sulfides to optically active sulfoxides has been performed using chiral organic peroxyacids. The first examples of the synthesis of chiral sulfoxides involved the asymmetric oxidation of alkyl aryl sulfides using (+)-(S)-peroxycamphoric acid, yielding high conversions and low enantiomeric excesses.[204,205] Subsequently, other chiral mono- and dicarboxylic peroxyacids, such as monoperoxyglutaric acid,[206] have been used as well. As in the previously mentioned examples, high yields of sulfoxide resulted with low enantiomeric excesses.

In this work, the oxidation of thioethers was performed using the in situ generated organic peroxyacid derived from the reaction of maleic anhydride with the much safer 30% aqueous H_2O_2 in the solvent 1-methyl-2-pyrrolidinone. These sulfide oxidations were run in the absence and in the presence of transition metal catalysts. The metal-catalyzed reactions are described using a recently developed classification scheme[26,27] for the metal-catalyzed oxidations of organic substrates.

Results and Discussion

Activation of H_2O_2 by Maleic Anhydride

Using 1-methyl-2-pyrrolidinone as the solvent, an oxidative system involving the activation and stabilization of H_2O_2 was investigated using the peroxyacid preucrsor, maleic anhydride, under ambient conditions. When maleic anhydride and 30% aqueous H_2O_2 are mixed in the solvent 1-methyl-2-pyrrolidinone, the reaction is thought to involve the conversion of H_2O_2 into peroxymaleic acid (Figure 5-2). This conversion is greatly enhanced by the dehydrating ability of the solvent.[2] A subsequent stability study of the in situ peroxyacid in 1-methyl-2-pyrrolidinone under ambient conditions for 168 hours showed a notable stability (Table 5-1). This observed stability in 1-methyl-2-pyrrolidinone could be due to intermolecular interactions between the oxidant and the solvent.

This stable oxidizing system was found to be an effective oxidant of the thioether, n-butyl sulfide, resulting in the complete oxidation of an approximate 0.2 M solution in 1 hour. Both the reaction time for the complete oxidation to the sulfone and the selectivity to sulfoxide can be varied by changing the amount of H_2O_2. For example, decreasing the amount of H_2O_2 from 4.9×10^{-1} M to 1.6×10^{-1} M led to 100% yield in 14 hours (Table 5-2). The molar ratio of substrate to H_2O_2 was 1:1 in this reaction, demonstrating the efficient use of H_2O_2 in this sulfide oxidation. A 10:1 molar ratio of maleic

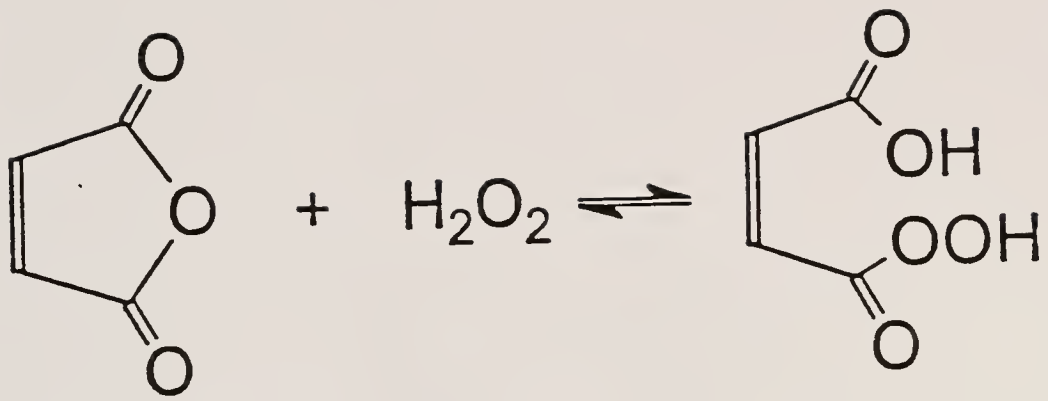


Figure 5-2 Formation of Peroxymaleic Acid in 1-Methyl-2-pyrrolidinone.

Table 5-1 Stability of Peroxymaleic Acid in 1-Methyl-2-pyrrolidinone.

Time (hours)	[ROOH], M
0	0.49
24	0.49
96	0.48
168	0.47

Note: Reaction conditions:
MA (1.6×10^{-2} moles)
H_2O_2 (4.9×10^{-3} moles, 30% aqueous solution)
NMP (10 mL)
run under ambient conditions.

Table 5-2 H_2O_2 Variation in n-Butyl Sulfide Oxidations Using Maleic Anhydride and H_2O_2.

Moles of H_2O_2	Time (min.)	Products (%)
$1.6x10^{-3}$	5	R_2SO (12)
	30	R_2SO (21)
	60	R_2SO (29)
	240	R_2SO (62)
	360	R_2SO (79)
	600	R_2SO (94)
	720	R_2SO (97)
	840	R_2SO (100)
$4.9x10^{-3}$	5	R_2SO (62)
	30	R_2SO (38) R_2SO_2 (62)
	60	R_2SO_2 (100)

Note: Reaction conditions:
substrate ($1.6x10^{-3}$ moles)
MA ($1.6x10^{-2}$ moles)
NMP (10 mL)
H_2O_2 (30% aqueous solution)
run under N_2 at ambient conditions.

anhydride to H_2O_2 was used in this experiment. Likewise, in a separate experiment, an increase in the amount of H_2O_2 to $4.9x10^{-1}$ M resulted in the complete oxidation of sulfide to sulfone in 1 hour. It is interesting to note that an analogous reaction employing no maleic anhydride showed only a 7% conversion to sulfoxide, clearly demonstrating the involvement of a much stronger oxidant, such as a peroxyacid in the previous reaction.

The use of a less reactive thioether, diphenyl sulfide, with the maleic anhydride/H_2O_2 system led to the complete oxidation of the substrate to sulfoxide (14%) and sulfone (84%) in 1 hour. No oxidation products were observed in an analogous reaction containing no maleic anhydride.

Catalytic Maleic Anhydride

Further experimentation has demonstrated that maleic anhydride is catalytic in the oxidation of n-butyl sulfide with these systems. Various 1:1 H_2O_2 to substrate molar ratios were studied at ambient conditions, at molarities two to three fold that of maleic anhydride (Table 5-3). After 5 minutes of reaction, complete oxidation of the substrate was observed. The results obtained for these experiments show >100% efficient use of H_2O_2; thereby, suggesting the involvement of another oxidant in these systems. The addition of the H_2O_2 to these solutions, containing the acid anhydride and the substrate, results in a very exothermic reaction, with temperatures of >75°C being observed. Since the reaction

Table 5-3 n-Butyl Sulfide Oxidations Using Catalytic Amounts of Maleic Anhydride.

Moles of $n\text{-}Bu_2S$	Time (min.)	Products (%)
3.2×10^{-2}	5	R_2SO (73) R_2SO_2 (27)
5.0×10^{-2}	5	R_2SO (67) R_2SO_2 (33)

Note: Reaction conditions:
substrate:H_2O_2 (1:1)
NMP (4.2 mL)
MA (1.6×10^{-2} moles)
run under ambient conditions in air.

vessels were open to the atmosphere, it is most likely that the solvent, 1-methyl-2-pyrrolidinone, reacted with atmospheric oxygen to form the corresponding N-alkylamide hydroperoxide, which would result in the further oxidation of the sulfide and/or sulfoxide. Under an N_2 atmosphere, an analogous reaction showed a 97% efficient use of the H_2O_2 (Table 5-4). When compared with a blank run containing no maleic anhydride a much greater rate of oxidation occurred (Table 5-4), providing further support for a more stable and stronger oxidant, peroxymaleic acid.

Effect of Transition Metal Catalysts

The activation of H_2O_2 in the solvent, 1-methyl-2-pyrrolidinone, was pursued using the peroxyacid precursor, maleic anhydride, in the presence of transition metal catalysts. The addition of maleic anhydride to the solvent, 1-methyl-2-pyrrolidinone, enabled H_2O_2 to oxidize n-butyl sulfide completely to the corresponding sulfone in 1 hour without the use of metal catalysts (Table 5-5). Several transition metal catalysts investigated showed an enhancement in the activity with this system.

The addition of $Mo(O)_2(acac)_2$ to the maleic anhydride/H_2O_2 system led to complete oxidation of the sulfide to the corresponding sulfone in 5 minutes (Table 5-5). It is interesting to note that the analogous reaction containing no maleic anhydride required a substantially longer reaction time

Table 5-4 n-Butyl Sulfide Oxidations Using Catalytic Amounts of Maleic Anhydride.

Moles of MA	Time (min.)	Products (%)
none[a]	5	R_2SO (9)
	30	R_2SO (16)
	60	R_2SO (33) R_2SO_2 (1)
$1.6x10^{-2a}$	5	R_2SO (73) R_2SO_2 (27)
$1.6x10^{-2b}$	5	R_2SO (75) R_2SO_2 (11)

Note: Reaction conditions:
substrate ($3.2x10^{-2}$ moles)
H_2O_2 ($3.2x10^{-2}$ moles)
NMP (4.2 mL)
run under ambient conditions.

a. Under air.

b. Under N_2.

Table 5-5 Transition Metal-Catalyzed n-Butyl Sulfide Oxidations Using Peroxymaleic Acid.

Catalyst	Time (min.)	Products (%)
none	5	R_2SO (35) R_2SO_2 (57)
	30	R_2SO (10) R_2SO_2 (88)
	60	R_2SO_2 (100)
$CoCl_2 \cdot 6H_2O$	5	R_2SO (8) R_2SO_2 (88)
	30	R_2SO (8) R_2SO_2 (90)
	60	R_2SO (8) R_2SO_2 (90)
$FeCl_3 \cdot 6H_2O$	5	R_2SO (31) R_2SO_2 (66)
	30	R_2SO (32) R_2SO_2 (68)
	60	R_2SO (32) R_2SO_2 (68)
$RuCl_3 \cdot 3H_2O$	5	R_2SO (2) R_2SO_2 (93)
	30	R_2SO (1) R_2SO_2 (98)
	60	R_2SO_2 (100)
$Mo(O)_2(acac)_2$	5	R_2SO_2 (100)

Table 5-5--Continued.

Catalyst	Time (min.)	Products (%)
$V(O)(acac)_2$	5	R_2SO (60) R_2SO_2 (40)
	30	R_2SO (60) R_2SO_2 (40)
	60	R_2SO (60) R_2SO_2 (40)
$ReCl_3$	5	R_2SO (2) R_2SO_2 (92)
	30	R_2SO (1) R_2SO_2 (99)
	60	R_2SO_2 (100)
$NiCl_2 \cdot 6H_2O$	5	R_2SO_2 (100)

Note: Reaction conditions:
substrate (1.6×10^{-3} moles)
H_2O_2 (4.9×10^{-3} moles, 30% aqueous solution)
MA (1.6×10^{-2} moles)
NMP (10 mL)
run under N_2 at ambient conditions.

to totally oxidize the sulfide to the sulfone (Table 5-6). The reactivity seen with this catalyst indicates Class IVb behavior.[26,27]

Complete oxidation of the sulfide to the corresponding sulfone was observed in 5 minutes with the metal salt, $NiCl_2 \cdot 6H_2O$, in the peroxyacid system. The formation of a metal acylperoxo complex as the active catalytic species is most likely responsible for the Class IVb[26,27] behavior exhibited (Table 5-5). The use of H_2O_2 as the oxidant in an analogous reaction with this catalyst showed a much lower substrate conversion to the corresponding sulfoxide and sulfone (Table 5-6). Using H_2O_2 as the oxidant, this nickel(II)-catalyzed system exhibits Class IVb behavior with a non-productive Class IVa component.[26,27]

The catalyst, $RuCl_3 \cdot 3H_2O$, showed less activity than the analogous molybdenum(VI)- and nickel(II)-catalyzed reactions (Table 5-5). This decreased activity resulted from the non-productive metal-catalyzed peroxyacid decomposition (Class IVa).[26,27] When compared with the analogous reaction using H_2O_2 as the oxidant (Table 5-6), the maleic anhydride/ ruthenium-catalyzed oxidation exhibits an increase in oxidative activity.

The thioether, n-butyl sulfide, was oxidized by the peroxyacid oxidant in the presence of a catalytic amount of $ReCl_3$ in a manner analogous to the above discussed $RuCl_3 \cdot 3H_2O$-catalyzed thioether oxidation (Table 5-5). A comparison of the results for the rhenium-catalyzed oxidations of n-butyl

Table 5-6 Transition Metal-Catalyzed Oxidations of n-Butyl Sulfide Using H_2O_2.

Catalyst	Time (min.)	Products (%)
none	5	R_2SO (5)
	30	R_2SO (7)
	60	R_2SO (7)
$CoCl_2 \cdot 6H_2O$	5	R_2SO (37)
	30	R_2SO (37)
	60	R_2SO (37)
$FeCl_3 \cdot 6H_2O$	5	R_2SO (53) R_2SO_2 (46)
	30	R_2SO (47) R_2SO_2 (53)
	60	R_2SO (47) R_2SO_2 (53)
$RuCl_3 \cdot 3H_2O$	5	R_2SO (75) R_2SO_2 (20)
	30	R_2SO (75) R_2SO_2 (20)
	60	R_2SO (75) R_2SO_2 (20)

Table 5-6--Continued.

Catalyst	Time (min.)	Products (%)
$Mo(O)_2(acac)_2$	5	R_2SO (68) R_2SO_2 (31)
	30	R_2SO (58) R_2SO_2 (41)
	60	R_2SO (46) R_2SO_2 (54)
	360	R_2SO (25) R_2SO_2 (75)
	1440	R_2SO (3) R_2SO_2 (97)
	2880	R_2SO_2 (100)
$V(O)(acac)_2$	5	R_2SO (15) R_2SO_2 (81)
	30	R_2SO_2 (100)
$ReCl_3$	5	R_2SO (40) R_2SO_2 (7)
	30	R_2SO (56) R_2SO_2 (10)
	60	R_2SO (60) R_2SO_2 (13)
	360	R_2SO (67) R_2SO_2 (15)
	1440	R_2SO (68) R_2SO_2 (24)
	2880	R_2SO (68) R_2SO_2 (24)

Table 5-6--Continued.

Catalyst	Time (min.)	Products (%)
$NiCl_2 \cdot 6H_2O$	5	R_2SO (38) R_2SO_2 (8)
	30	R_2SO (41) R_2SO_2 (8)
	60	R_2SO (45) R_2SO_2 (8)
	360	R_2SO (47) R_2SO_2 (9)
	1440	R_2SO (52) R_2SO_2 (10)
	2880	R_2SO (52) R_2SO_2 (10)

Note: Reaction conditions:
substrate (1.6×10^{-3} moles)
catalyst (1.6×10^{-4} moles)
NMP (10 mL)
H_2O_2 (4.9×10^{-3} moles)
run under N_2 at ambient conditions.

sulfide using H_2O_2 and peroxymaleic acid suggests Class III behavior with a Class IVa component.[26,27]

Less activity was observed with the catalysts, $V(O)(acac)_2$ (Class III with a Class IVa component),[26,27] $CoCl_2 \cdot 6H_2O$ (Class IVa),[26,27] and $FeCl_3 \cdot 6H_2O$ (Class IVa)[26,27] (Table 5-5). With these catalysts, the metal-catalyzed peroxyacid decomposition becomes a contributing factor as seen by the decreased selectivity to sulfone. Even though an increase in oxidative activity was observed in these metal-catalyzed thioether oxidations using peroxymaleic acid, the roles of the transition metal complexes showed analogous behavior in the corresponding oxidations using H_2O_2 as the oxidant.

Experimental

Reagents and Equipment

The n-butyl sulfide, n-butyl sulfoxide, n-butyl sulfone, diphenyl sulfide, diphenyl sulfoxide, diphenyl sulfone, and 1-methyl-2-pyrrolidinone (HPLC Grade) were obtained from Aldrich Chemical Company and used as received. The metal complexes, $Mo(O)_2(acac)_2$, $V(O)(acac)_2$, $ReCl_3$, and $RuCl_3 \cdot 3H_2O$ were received from Aldrich Chemical Company as well. All other reagents and solvents were obtained from Fischer Scientific and used as received.

Peroxyacid concentrations were determined by iodometric titrations.[33]

CAUTION! Many peroxyacids are shock/temperature sensitive and should be treated as potentially explosive.

A Varian 3700 GC with an FID and Hewlett Packard 3390A integrator was used to analyze the reactions, using a 6 foot stainless steel column packed with Carbowax 20M (10%) on Chromosorb WHP (80/100 mesh) for the n-butyl sulfide oxidations and a 6 foot stainless steel column packed with SE-30 (3%) on Gas Chromosorb Q (80/100 mesh) for the diphenyl sulfide oxidations. The substrate(s) and product(s) were identified and quantified using known standards.

Peroxymaleic Acid Stability

Maleic anhydride (1.6g, 1.6×10^{-2} moles) and 1-methyl-2-pyrrolidinone (10 mL) were placed in a 100 mL round bottom flask equipped with magnetic stirring. After 5 minutes of stirring, H_2O_2 (4.9×10^{-3} moles, 30% aqueous solution) was added dropwise to the acid anhydride solution. After 1 hour of stirring, the colorless sokution was stored under ambient conditions. The peroxyacid solution was analyzed periodically by iodometric titrations.

H_2O_2 Variation Study

Maleic anhydride (1.6g, 1.6×10^{-2} moles) and 1-methyl-2-pyrrolidinone (5.0 mL) were placed in a 100 mL round bottom flask equipped with magnetic stirring and an N_2 atmosphere. After 5 minutes of stirring, the appropriate amount of H_2O_2 (see Table 5-2) was added dropwise to the acid anhydride

solution. The resulting colorless solution was stirred for 1 hour to ensure formation of the peroxyacid.

1-Methyl-2-pyrrolidinone (5.0 mL) and n-butyl sulfide (0.23g, 1.6×10^{-3} moles) were placed in a 100 mL round bottom flask equipped with magnetic stirring and an N_2 atmosphere. After 30 minutes of stirring, the previously prepared peroxyacid solution was added dropwise to the reaction solution. Samples were analyzed periodically by GC.

Sulfide Oxidations Using Catalytic Amounts of Maleic Anhydride

The appropriate amounts of maleic anhydride, n-butyl sulfide, and 1-methyl-2-pyrrolidinone (see Tables 5-3 and 5-4) were placed in a 100 mL round bottom flask equipped with magnetic stirring and the appropriate atmosphere (see Tables 5-3 and 5-4). After 5 minutes of stirring, the appropriate amount of H_2O_2 (see Tables 5-3 and 5-4) was added to the reaction solution, giving an exothermic reaction. Samples were analyzed periodically by GC.

Metal-Catalyzed Sulfide Oxidations Using Peroxymaleic Acid

Maleic anhydride (1.6g, 1.6×10^{-2} moles) and 1-methyl-2-pyrrolidinone (5.0 mL) were placed in a 100 mL round bottom flask equipped with magnetic stirring and an N_2 atmosphere. After 5 minutes of stirring, H_2O_2 (4.9×10^{-3} moles, 0.5 mL of a 30% aqueous solution) was added dropwise to the acid anhydride solution. The resulting colorless solution was stirred for 1 hour to insure formation of the peroxyacid.

1-Methyl-2-pyrrolidinone (5.0 mL), n-butyl sulfide (0.23g, $1.6x10^{-3}$ moles), and the appropriate catalyst ($1.6x10^{-4}$ moles) (see Table 5-5) were placed in a 100 mL round bottom flask equipped with magnetic stirring and an N_2 atmosphere. After 30 minutes of stirring, the previously prepared peroxyacid solution was added dropwise to the reaction solution. Samples were analyzed periodically by GC.

Metal-Catalyzed Sulfide Oxidations Using H_2O_2

1-Methyl-2-pyrrolidinone (10 mL), n-butyl sulfide (0.23g, $1.6x10^{-3}$ moles), and the appropriate catalyst ($1.6x10^{-3}$ moles) (see Table 5-6) were placed in a 100 mL round bottomed flask equipped with magnetic stirring and an N_2 atmosphere. After 30 minutes of stirring, H_2O_2 ($4.9x10^{-3}$ moles, 0.5 mL of a 30% aqueous solution) was added dropwise to the reaction solution. Samples were analyzed periodically by GC.

Conclusions

Thioethers, such as n-butyl sulfide, can be oxidized to the corresponding sulfoxides and sulfones in the solvent, 1-methyl-2-pyrrolidinone, using maleic anhydride to activate H_2O_2 under ambient conditions. The active oxidant in this oxidative system, peroxymaleic acid, exhibited an exceptional stability in 1-methyl-2-pyrrolidinone under similar conditions. When compared with the analogous thioether oxidations using H_2O_2, the addition of maleic anhydride to these reactions resulted in a very pronounced increase in activity.

Furthermore, the use of a catalytic amount of the acid anhydride in reactions employing 1:1 molar ratios of H_2O_2 to substrate exhibited a 97% efficient use of the H_2O_2; therefore, demonstrating the catalytic formation of the organic peroxyacid.

Further work in the activation of H_2O_2 in the solvent, 1-methyl-2-pyrrolidinone, using the peroxyacid precursor, maleic anhydride, was pursued using catalytic amounts of transition metal complexes. These transition metal catalysts showed an enhancement in the activity over the analogous peroxyacid system containing no metal catalyst. When compared with the analogous metal-catalyzed reactions using the oxidant, H_2O_2, these metal-catalyzed reactions using peroxymaleic acid as the oxidant required much shorter reaction times for the oxidation of the substrate.

When using either of these oxidants (H_2O_2 or peroxymaleic acid), the role of a particular metal catalyst appears to be identical. For example, $Mo(O)_2(acac)_2$ exhibits Class IVb[26,27] type reactivity using either oxidant in the oxidation of n-butyl sulfide, while $CoCl_2 \cdot 6H_2O$ shows Class IVa[26,27] behavior.

CHAPTER 6
GENERAL CONCLUSIONS

Approximate 2M solutions of the stable N-alkylamide hydroperoxide, 5-hydroperoxo-1-methyl-2-pyrrolidinone, can be produced by the reaction of 1-methyl-2-pyrrolidinone with molecular oxygen under mild conditions. When reacted with an organic substrate, the oxygen atom transfer from the hydroperoxide to the substrate produced the amido-alcohol intermediate, 5-hydroxy-1-methyl-2-pyrrolidinone. In the presence of molecular oxygen, the amido-alcohol intermediate underwent rapid oxidation to N-methylsuccinimide. Using the appropriate transition metal catalyst, N-methylsuccinimide can be hydrogenated under mild conditions to yield the hydroperoxide precursor, 1-methyl-2-pyrrolidinone. The use of 1-methyl-2-pyrrolidinone in a catalytic cycle employing molecular hydrogen and oxygen in the presence of transition metal catalysts provides a regenerative hydroperoxide system for organic substrate oxidations.[24,25]

Under mild conditions, alkenes, such as trans-β-methylstyrene and 1-hexene, can be selectively oxidized to the corresponding epoxides using the N-alkylamide hydroperoxide, 5-hydroperoxo-1-methyl-2-pyrrolidinone. Both the completion times and the product selectivities are dependent on the nature of the transition metal catalyst. Higher selectivity

to epoxide formation and less efficient alkyl hydroperoxide utilization were observed with radical-chain catalysts (Class IVa).[26,27] The use of metal oxo complexes results in a substantial lowering of the selectivity to epoxide. These catalytic systems exhibited a lower stereoselectivity in the formation of epoxide as well.

Further investigations into the $Mo(O)_2(acac)_2$-catalyzed oxidations of cis- and trans-β-methylstyrene have shown that this metal complex exhibits Class IVb behavior.[26,27] The stereoselectivity (or lack of) in the formation of epoxides was found to exhibit a pronounced dependency on the polarity of the solvent. Spectroscopic evidence supports the involvement of a more selective triangular metal alkylperoxo species in non-polar solvents and a less selective linear metal alkylperoxo species in polar solvents.

In the presence of catalytic amounts of pyridine, the molybdenum-catalyzed oxidations of cis- and trans-β-methylstyrene resulted in the increased formation of the corresponding epoxides. The pyridine appears to facilitate the dissociation of the epoxide from the metal-containing intermediate via facile coordination to the molybdenum center.

Thioethers can be oxidized to the corresponding sulfoxides and sulfones in the solvent, 1-methyl-2-pyrrolidinone, by either the activation of molecular oxygen under mild conditions, or the activation of hydroperoxides under ambient conditions. The in situ generated N-alkylamide hydroperoxide system exhibited shorter reaction times and less

efficient utilization of the alkyl hydroperoxide using radical-chain catalysts (Class IVa),[26,27] while the use of metal oxo complexes that bind the hydroperoxide (Class IVb)[26,27] showed longer reaction times and a more efficient use of the alkyl hydroperoxide.

In the presence of transition metal catalysts, alkyl hydroperoxides, 5-hydroperoxo-1-methyl-2-pyrrolidinone and t-butyl hydroperoxide, showed comparable reactivity in the solvent, 1-methyl-2-pyrrolidinone, under ambient conditions. When compared with the analogous metal-catalyzed oxidations using H_2O_2, these reactions exhibited a lower activity in 1-methyl-2-pyrrolidinone.

Another oxidative system involving the activation and stabilization of H_2O_2 was investigated using the peroxyacid precursor, maleic anhydride in the solvent 1-methyl-2-pyrrolidinone. When compared with the analogous thioether oxidations using H_2O_2, the addition of maleic anhydride to these reactions resulted in a very pronounced increase in activity. Further experiments demonstrated the catalytic formation of the organic peroxyacid in 1-methyl-2-pyrrolidinone.

When compared with the analogous uncatalyzed reactions, the employment of transition metal complexes in the peroxymaleic acid oxidative system showed an enhancement in the activity. These metal-catalyzed thioether oxidations exhibited much shorter reaction times than the analogous metal-catalyzed reactions using H_2O_2 as well.

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BIOGRAPHICAL SKETCH

Douglas E. Patton, son of Critinton Lawrence and Shirley Jo (Jordan) Patton, was born January 14, 1958, in Montgomery, Alabama. He received the Eagle Scout Award, the Bronze Palm Award, and the God and Country Award while in the Boy Scouts of America. He attended Sidney Lanier High School in Montgomery, Alabama, and finished in May, 1976. In September, 1976, he entered Auburn University at Montgomery. He transferred to Auburn University in Auburn, Alabama, in September, 1978. In June, 1986, he received the degree of Bachelor of Science (Chemistry). He entered graduate school in chemistry at Auburn University in September, 1986, working under Professor William E. Hill. In December, 1988, he received the degree of Master of Science (Chemistry). He entered graduate school in chemistry at the University of Florida in August, 1988, working under Professor Russell S. Drago. In April, 1992, he married Lynn Rabon. He is presently a member of the American Chemical Society.

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